Pathology علم الأنسجة

أنواع الـ microabsces

Q/ nail psoriasis

Q/ Koebner ---

Q/ psoriatic Arthrito-

Q/ Pustular Ps. → pregnancy

* methotrexate
+ cyclosporine

Psoriasis

Def.: Common, chronic, idiopathic inflammatory skin disorder with unpredictable remission and relapse. (Serious & SYS Fem/C)

Epidemiology:

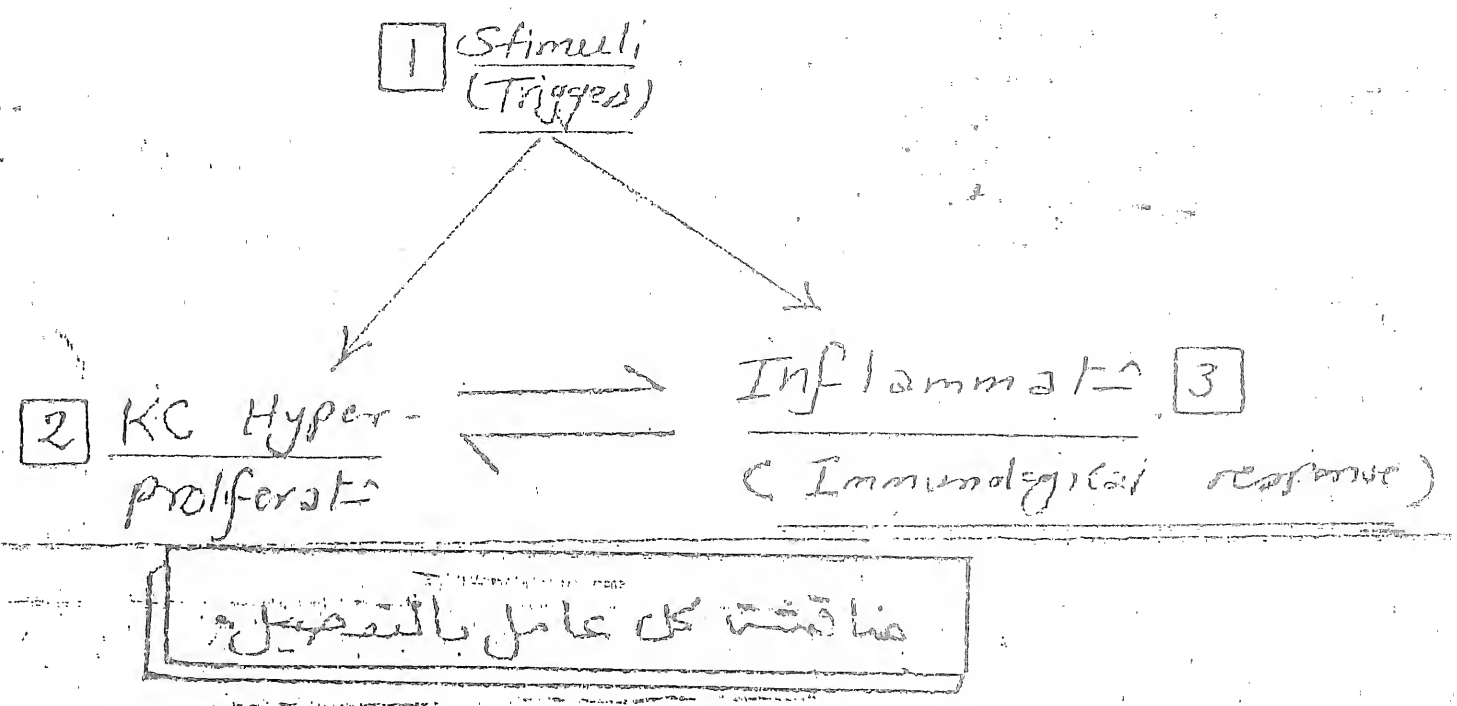
Incidence: 1-2% of general populations.

Age: any, but commenest between (15-40 Ys). (mean 28 Y).

Sex: no predilection.

Pathogenesis of psoriasis
(Hunter's dermatology 2008)

The Exact Etiopathogenesis is unknown but there are 3 key Features (Triad) & interacts with each others.



مناقشة كل عامل بالتفصيل:

A. Triggers (Stimuli) of Ps.:

1. Genetics:

- There are 2 Types of Ps. Acc. to the Inheritance Mode (see the table).

Inheritance is polygenic & Genetic loci are:

- Psor S1 (Chromosome 6).
- Psor S2 (" 17).

- Typical of HLA < B13 & Cw6 (Early onset Ps.)
  B27 (Pustular Ps & Ps. arthropathy).

- FH in Ps. Ch BY:
  - +ve in 30% of cases.
  - if 1 parent affected ⟶ 16% Chance of offspring Affection.
  - if 2 parents affected ⟶ Chance of 50%.

If one of my parents has psoriasis, what's the chance that I'll get psoriasis?

والأب أخطر من الأم في التوريث (Genetic imprinting)

- Twins affected:
  - MonoZygotic (متماثل) → 73%.
  - DiZygotic (غير متماثل) → 20%.

- Types of Ps:

	Type I (Commonest)	Type II (less common)
Onset	Early (20 y.)	Late (50-60 y.)
Course	More generalized & Severe	Mixed & Localized
FH	Common	Rare
HLA	Cw6 (Frequently)	Rare

2. Trauma: → d.t Koebner phenomenon.
3. Infect: → Streptococci may act as a Superantigen
   - usually: pharyngitis & ± dental inf.
   both may ⟶ Plt. of pustular Ps., Exacerbate of plaque Ps. & Flare of Guttate.
4. Stress: → release substance P ⟶ Neurogenic inflamm. (Sx Capsiacin may be used in HH).
5. Drugs: → Drug induced Ps. lithium, BBr, Antimalarial, TKN
6. Climatic: → Ps. improves ↑ Summer & Exacerbate in winter. (Wbr).
7. Hormones:
   - Ps ↑↑ by: Puberty, Menopause & Hypocat
   - Ps ↓↓ by: pregnancy (±).

(8.) KC Hyperproliferation (↑↑ Epidermopoiesis)

(Epidermal Cell Kinetics in Psoriasis)

2 important Events

- ↑↑ growth Fraction. (GF)
  - ↑↑ No of germinative cells That enter the Cell Cycle (60% in PS Compared to 30% of Basal KCs in NL Skin).
- Shortened Epidermal renewal Time (Turnover).
  - in NL Skin it is 30-60 ds. while in Psoriatic Skin it ↓↓ to ≤ 7-10 ds.

[الوقت اللي بأخذه خلايا الـ Basal KCs إلى ما تصير corneocyte وتكون جزء من الـ SC]

Both → out of control Prolif. (Hyperprolif).

- Exceeds capacity of desquamation → ↑ rate.
- retent of Nuclei → Parakeratosis

KC. Etiology & mechanism of Hyperprolif: unknown but 1 d.f;

① ↑ HS Wound healing like process & So;
- cGMP, NO-synthase, Polyamines, Calmodulin all are ↑.

② Genetic defect in control of KC growth.
→ subNL activat° of Transcription Factors:
- STAT-1α (NL ↓↓ by IFN-γ)
- NFκB.

NB: Epidermopoesis → Continous rate of epid. prolif.

- Turnover = Transit time: تزييت
- Growth Fraction: % of dividing Basal cells.

∴ Epidermopoesis ↑ d.t either ↑ Growth Fraction or Shortened Transit time or Both.

(C) Inflammation

(Immunological Response ph ps).

Triggers (Inf., Trauma, Stress).

↓

++ KCs

↓ Secrete.

IL1

IL-8

NB. Also Attract Neut. to epid. → "Microabsces of Munro"

1. ↑↑ Expression of ICAM-1 & E Selectin on Vascular endothelium of papillary dermal BVs. →

Accomalatn of T-lymphocytes (CCLA+ve memory cells) (CD4) Their adhesion to Vascular Endoth. Through interaction of their LFA-1 with ICAM-1 & E Selectin on Vascular Endoth.

(ICAM) (E Selectin)

2. يبدأ تجمع T-cell في البابط Endothelium of papillary dermal BVs

فالتتابع تتدرّك من خلال جدار الوعية الدموية الى داخل الـ Dermis وتفاعلها معه

T-cell Trafficking

IL8 → Attract T-lymphocytes into Dermis

where they (interact) with the:

(APCs) (LHCs).

↓

The interaction bet T-cells & APCs occurs through (3 Signals) & ends by T cells (Activation & differentiation)

(C) Inflammation

(Immunological Response in PS).

Triggers (Inf., Trauma, Stress).

↓

++ KCs

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1. ↑↑ Expression of ICAM-1 & E Selectin on Vascular endothelium of papillary dermal BVs. →

Accumulation of T-lymphocytes (CLA+ve memory cells) [CD4] Then adhesion to Vascular Endoth. Through interaction of their LFA-1 with ICAM-1 & E Selectin on Vascular Endoth.

(يؤدي للالتصاق بين الـ T-cell والـ Endothelium عن طريق الـ ICAM)

2. بعد تجمع الـ T-cell والتصاقها بـ Endothelium of Papillary dermal BVs

فإنها تبدأ بالهجرة من الأوعية الدموية إلى داخل الـ Dermis وهذه العملية تسمى

"T-cell Trafficking"

IL8 → attract T-lymphocytes into Dermis where they (interact) with the:

APCs (LHCs).

↓

The interaction between T-cells & APCs occurs through (3 signals) & end by T cells (Activation & differentiation)

T Cells are Activated by LCs Through 3 Sets of Signals

٣ تفاعلات بيحصل بين (LC) و (TC)

① 1st signal (Ag recognition): recognition of Ag Bound To MHC-II (on LCs) by TCRs (on T Cells)

(Ag) بتعرف على

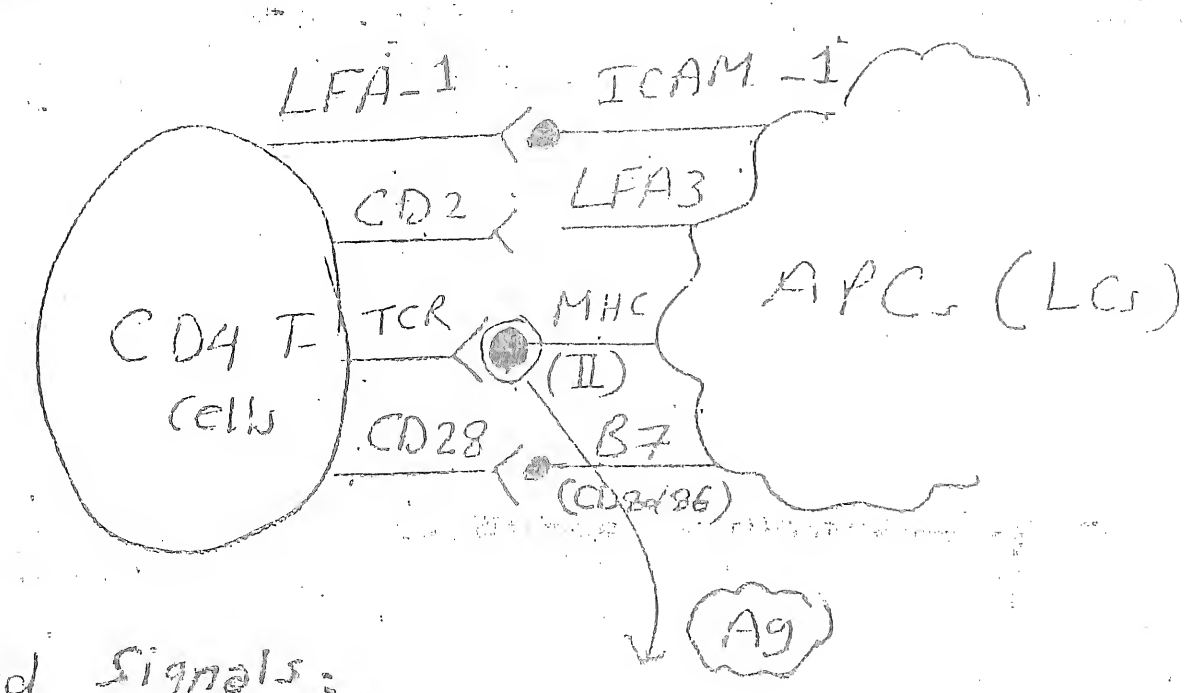
major histocompatibility complex

② Costimulatory Signals:

Coordinated stimulation of T Cells by Costimulatory molecules present on surface of APCs.

T Cells تنشيط

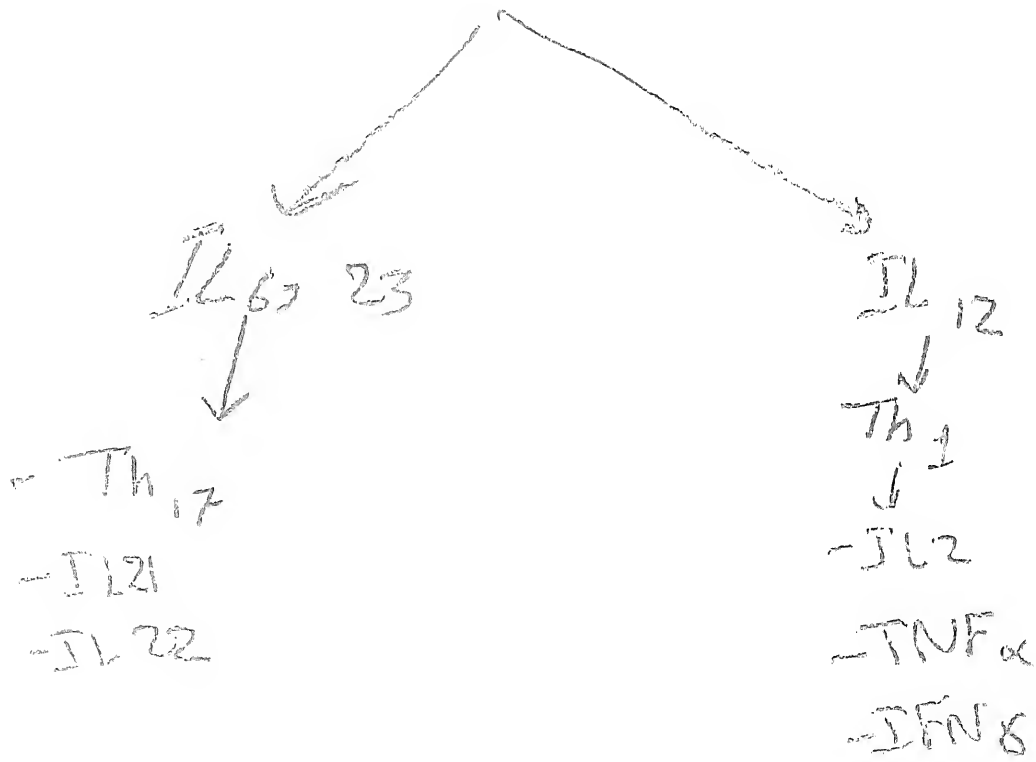
عن طريق استقبال LCs



③ 3rd Signals:

Cytokines release & Interaction with Their Receptors.

(Release of cytokines From APCs IL-6, IL-12 → CD4 differentiation)


IL-6, 23
IL-12
Th-17
Th-1
-IL21
-IL22
-IL2
-TNFα
-IFNδ

• Th17s :

Naive T cells (CD4 = T0 helper)

STAT3 activated by IL6/IL21 & responsible for IL17A IL17F expression

IL6, IL23 + TGFβ

IL12, IL18

differentials

Th17 ++

Th1

↓

↓

• IL17

• IL21

• IL22

hyperplasia

"KC Hyperprolif."

↓

Epid. renewal time ↓ From: (30-40 or 52-75) To < 10 ds.

• Type I Cyto. Kines :

• ++ T cell prolif. ← • IL2 (also IL18/12)

• KC Hyperprolif ← [• IFNγ, • TNFα

↓

• KCs Hyperprolif.

NB → IL8 → attract neutrophils to epid.

NB. The old saying that Ps is Th1 disease but recently it is (Th1 & Th17)

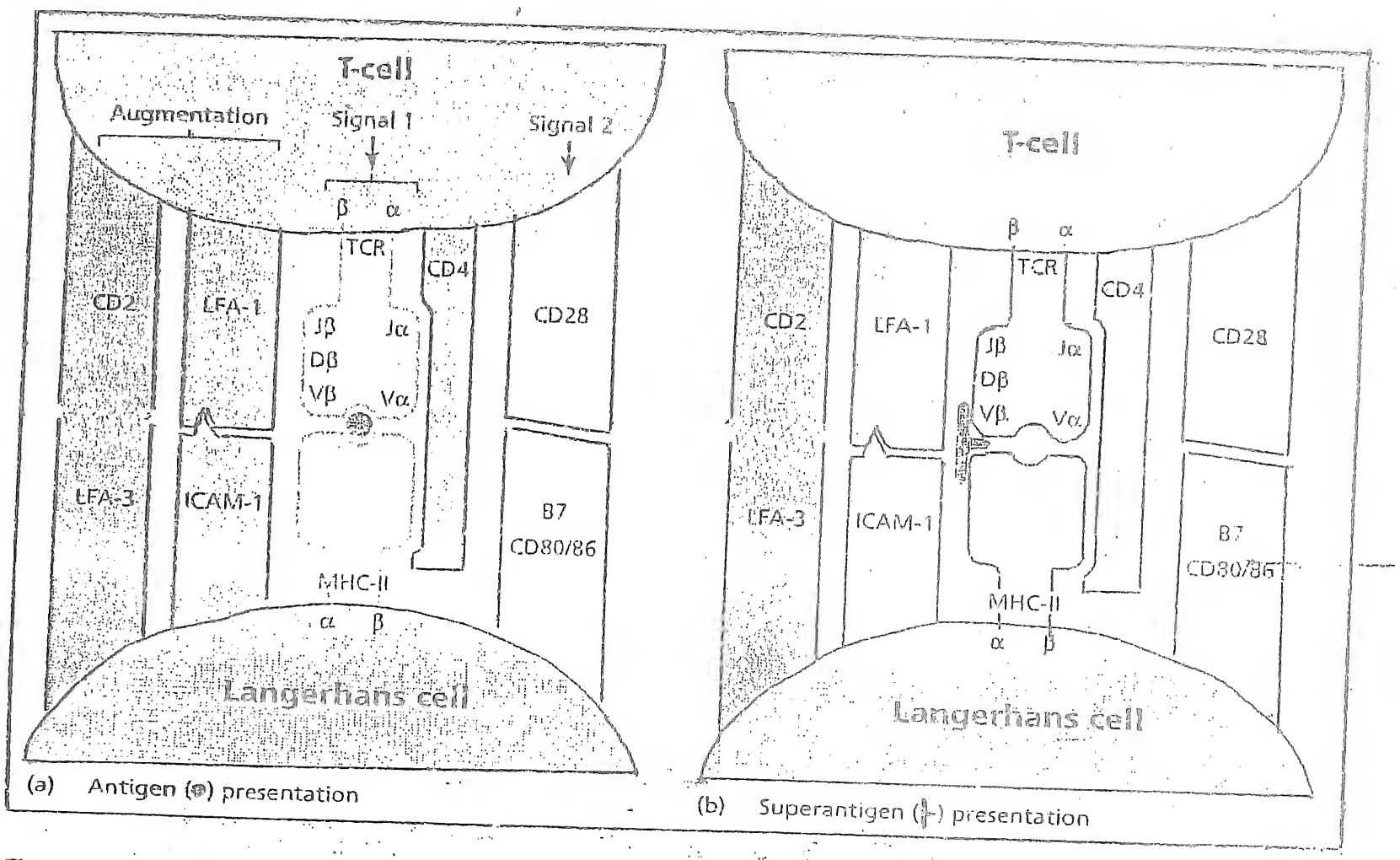


Fig. 2.12 T-lymphocyte activation by (a) antigen and (b) superantigen. When antigen has been processed it is presented on the surface of the Langerhans cell in association with major histocompatibility complex (MHC) Class II. The complex formation that takes place between the antigen, MHC Class II and T-cell receptor (TCR) provides signal 1, which is enhanced by the coupling of CD4 with the MHC molecule. A second signal for T-cell activation is provided by the interaction between the costimulatory molecules CD28 (T cell) and B7 (Langerhans cell). CD2/LFA-3 and LFA-1/ICAM-1 adhesion augment the response to signals 1 and 2. Superantigen interacts with the TCR Vβ and MHC Class II without processing, binding outside the normal antigen binding site. Activated T cells secrete many cytokines, including IL-1, IL-8 and interferon-γ, which promote inflammation (Fig. 2.13).

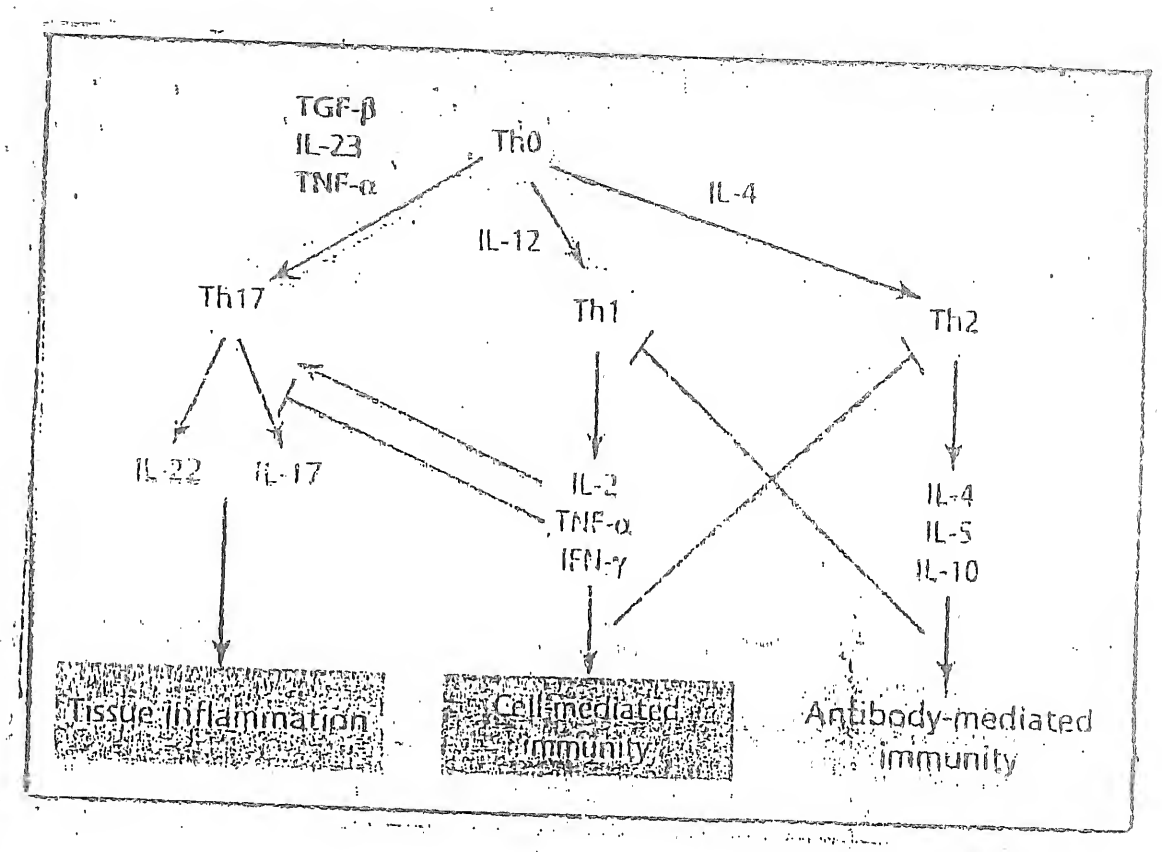


Fig. 2.13 Characteristics of Th1, Th2 and Th17 responses.

Clinical Picture of Psoriasis

- Psoriasis may affect:
  - Skin
  - Eye (ocular Psoriasis)
  - NM
  - Hair
  - Nail
  - Joint.

- The Most Important systemic Association are:
  (1) Ps. Arthritis (2) Metabolic Synd.

(A) Psoriasis of Skin:

Classical Type

(Ps. vulgaris = plaque ps)

- SubTypes (varieties): - according to shape 1-8
  - acc. to site A

(1). Guttate
(2). Annular
(3). linear
(4). nummular — most common form
Geographic
(6) Ruporid
(5) follicular
(6) Elephantine
(7) ostraceous
(A) Flexural (Inverse ps).
(C) pp (palmoplantar)
(B) scalp.
(E) sub. ps.
(D) nail ps.
(F) mucosal

- Ps. vulgaris = chr. plaque Ps.: "Plaques Ch-By":
  - well defined, raised, Erythematous, Asympt. or itchy, Covered & Silvery scales.
  - Sites: any site but Commonest: Extensor surfaces, Elbows, Knees, sacral & scalp.
  - Grattage Test: Scraping of psoriatic lesions with edge of glass slide → removal of scales layer after layer till a thin membran (Duckett's memb.) is reached → on its removal → Pin Point Bleeding occurs (Auspitz Sign).

Variants of Ps.

- Drug induced
- Pustular Ps.
- Erythrodermic Ps.
- unstable Ps. (Phases in the dis. & unpredictable Course & marked activity).

- What is Auspitz Sign & what its Cause:

- it is a pin point Hgic spots induced by Gratage test; representing the excoriations of the Thin Supra papillary portions & exposure of dilated Vs on tip of dermal papillae.

- Subtypes of Ps. Vulgaris:

1. Guttate (water drops): Ch BY:
   - Abrupt onset.
   - Following Strept. inf.
   - usually < 30 Y/o & Children.
   - Rx → of Ps. + Antibiotics or Tonsillectomy.
   - prognosis → good in children & chronic in adults.
2. Annular: d.t central clearing of plaque or Coalescence of multiple papules.
3. Nummular: Coin Shapped.
4. Linear: d.t Koebner phenomenon.
5. Geographic: Curved patterns.
6. Rupoid: Heavily crusted (Simulating Ss Rupia) "Ostraceous"
7. Flexural (Inverse or Intertrigenous Ps.):
   - affect intertrigenous areas ??
   - Clp → well defined Erythema
     but usually ↓ Scaling (d.t Moisture)
     Itching is marked.
8. Palmoplantar: → many patterns
   - Silvery, scaly patches + Erythema.
   - Fissured, thick plaques.
   - Pustular.
   - Rupoid: Crusted, Hard lamellar, Oyster shell-like

differentiated from ECZ. by Sharp Margins at Wrist.

9. Scalp Psoriasis: → Several patterns:

ⓐ. diffuse (Erythema + silvery scaling).

ⓑ. discrete discoid plaques

Corona ← ⓒ. Corona Psoriatica: "Ant. Hair line involvem."

ⓓ. Pityriasis Amiantacea.

ⓔ Sebopsoriasis.

NB: (1.) Pityriasis Amiantacea:

. descriptive term (not a dis.) denoting

soft patches with (Firm) adherent

asbestose like scales (hair is matted)

Etiology: ± 2ry bact. inf. occuring on

top of:

. Eczema: AD or SD.

. Psoriasis or

. T. Capitis.

Hx: ① Topical Keratolytics: تقشير الجلد

② Shampooing ē: Tar, S or Selenium

help separat: of crust & improve inf.

85 Cases Studied:
- 35% → Ps
- 35% → Ecz.
- 13% → T. capit.

↓

Psoriasis is the most common cause

(2) Sebopsoriasis: Term applied to psoriatic lesions involving the scalp, eye brow, Ears

ⓦ have features of both diseases (Ps. or SD) or changin during the course. Behave as Ps. & SD.

(3) DD from SD:

Ps: dry silvery scales
Marginal involvement
Mild itching
± Hair loss.

SD: greasy, large scales
diffuse involvem.
Marked itching
No hair loss.

NB: PS. is more itchy in the following conditions: 1. Flexural PS.
2. Psychogenic disturbance
3. CD of Topicals.

(B) PS. of The MM.:

MM is not involved in PS. Except in the Scaly of pustular & Erythrodermic Types; varieties:

- Silvery Scaling of lips.
- Gray or White Plaques.
- Annular lesions.
- Geographic Tongue. ⟶ (Annulus Migrans).

• Geographic Tongue:
2 Varieties:
(1) Circinate or annular raised white lines
(2) Irregular, Map like, red glazed swollen patches surr. by White-border

→ Bg Migratory Glossitis.

(C.) Nail Psoriasis: (Most)

Causes
- NL Popul. (2%)
- Familial
- PS.
- Atopy
- DM
- Anemia
- Reactive arthritis.

(Andrews' Dx)

Incid.:
1. occurs alone in (5-10%) of cases.
2. May associate Cut. PS. in (25-50%) of Cases.
3. ↑ be associated ± PS. Arthritis in (50-75%).

Psoriasis may affect:
- Nail bed.
- Nail Matrix

Manifestations: ± dt ⟵ Matrix affect / Bed affect

(A) Matrix affect:

- Pitting (dt Parakeratosis) (most)
- Beau's lines
- Ridging
- Leukonychia (True)
- Spotted Lunula (Erythematous lunula)

Most common → Pitting / Oil Spot- → most diagnostic

• Crumbling & dystrophy.

(B) Bed affect: (1) Oil spot or drop sign:

Yellow-red Circular, Translucent areas (d.t hemosiderin) 2° to RBCs beneath the plate.

NB

- Other causes of nail pitting ??
  - Traumatic
  - Alopecia areata
- How to differentiate ??

Ps. pitting { Large deep randomly arranged
Other Pitting { Small uniform arranged in cross hatched pattern.

(E) Eff of Nail Ps

- Mild affect (ILs, Dermovate, Taz. under occlusion, Diar., 5FU)
- Severe affect: MTX, CyA, Acit, Biologics.

2. Subungual Hyperkeratosis
3. onycholysis.
4. Splinter Hge: longitudinal dark red lines due to minute foci of capillary Hge (Auspitz sign),
5. yellowish discolorat (d.t Serum lipoprotein deposit)
6. Leukonychia apparent

(A) distal DD
- Trauma
- Ps.
- onychom.

N.B; Proximal: Systemic
- Endocarditis
- Vasculitis
- Aps.

(D) Ps. of the Hair:
(Follicular Ps.)

- Prominent follicular involvement mainly on thighs, Elbows & Knees.

(E) Ps. of the Joints
(Psoriatic Arthritis).

- Incidence:
  - May be the only manifs in (10-15%) of cases.
  - Ass. with Cut. Ps. in (25-30%)
  - Ass. with nail Ps in (50-75%)
- Types:

Type I - Classic distal interphalangeal joint involvement (5% of patients)

Type II - Arthritis mutilans (Ass. ± bone resorpt & soft tissue collapse).

Type III - Symmetric polyarthritis (Rhmd like of Hands, Feet, Knee, Elbow).

Type IV - Asymmetric oligoarthritis (the most common type of psoriatic arthritis, occurring in 70% of patients) [≃ 4 large joints affected ± c MTP, PIP & DIP affect → sausage digit]

Type V - Ankylosing spondylitis
- Arthritis of spine → lipping or Vertebral fusion (rigid or bamboo spine).

- Treatment
  1. NSAIDs ✓
  2. DMARDs
     - MTX
     - CyA
     - Leflunamide
     - Antimalarial
     - Sulfasalazine
  3. Biologics ✓

DD: Reiter (Reactive) arthritis

- X Ray
  - Most important is erosive
  - Changes of Terminal phalanges (Acro osteolysis)
  - Tapering of phalanges at MC.
  - Cupping of proximal end of phalanges (Pencil in cup deformity)

NB: (مهم)

"or" Koebner (Isomorphic) phenomenon: (مهم)

Def. development ☡ the isomorphic pathologic lessons in the Traumatized uninvolved skin in patients who have a Cut. dis.

Incid. - Effect ≃ 25% ☡ psoriatic pts

onset - occurs after aperiod ☡ 2-6 wks following: Trauma, burn, Morbiliform Rash.

Rule - Follows all or non Rule (if ☡ occurs one area will occur in other all areas ☡ ant anatomic Preferences)

Mech. - Mech. unknown but ↓ d.t: Trauma that cause epid. & papillary dermal injury → ↑ EGF & their Receptors → Vascular & epid. changes.

Reverse Koebner: Trauma → disappearance ☡ Lesions. (in Ps & SA)

Koebner

* it occurs in:

- Ps
- L.P.
- PRP
- Vitiligo
- EM
- Plane wart
- Mollus cum
- Pellagra
- LS
- skin ← Darier, Kyrles, Kaposi

- What is Pseudokoebner phenomenon?

- Variants of Ps. Vulgaris:

1. Drug induced
2. Pustular.
3. Erythrodermic.

(1) Drug induced Ps: (see)

- NSAIDs
- ACEI
- BB
- CCB
- INF
- ILs

- Antimalarial → (Erythroderma)
- lithium
- systemic Cs (Pustular flare)

Pustular psoriasis

Def. psoriasis ē Macroscopic pustules. (Mac. accumulation of Neutrophils in epid.)

Types

Localized

(usually Localized to hands & feet)

1. Acute: → pustular bacterid
2. Chronic: → Palmoplantar - Pustulosis
3. Acrodermatitis Continua of Hallopeau

Generalized

1. Acute Generalized pustular psoriasis (Von-Zumbasch)
2. Pustular psoriasis ♀ pregnancy
3. Localized pattern (not involve hands & feet)
4. Annular pattern.
5. Exanthematic type
6. Infantile & Juvenile.

- Pustular Bacterid: Brief, Symmetrical, Acute eruption of "itchy" sterile pustules at palms & soles ē exacerbation & Remissions.

- start at mid portion of hands or feet → spread to affect the whole flexor aspect ♂ palm ♂ sole.

- AET + < Variant of acute exacerbation of PP. pustulosis
  Reaction: (1) Remote bacterial infection. (So called Bacterid)

(Diagnosis) → presence of Remote Bact. Inf. —when tt→ Resolution of the dis. (So tt is → Antibiotics + Antipsoriatics).

Palmoplantar Pustulosis (PP Pustulosis)

- Similar to Pustular bacterid but < no inf / More chronic
- dusky Red plaques → studied ē Many yellowish pustules → dissecate → exfoliate
- pustules are seen in all stages ∴ the dis as old ones heal ; New erupt. →
  ∴ the Condition Tend to be More chronic & persistent.
- May be ass. ē:
  - Thyroid disorders
  - Cigarette smoking
  - Lithium
  - S. A P(H.)O Syndrome.

Synovitis — acne (acneiform) — pustulosis

Hyperostosis & Osteitis:
- Sternoclavicular hyperostosis
- Pain & Swelling of sternoclavicular or costo-Chondral Joint

- Tt
  1. Topical < Cs, Tacrolimus, Dàivonex, Trchinoin
  2. Systemic < Acitretin, Etretinate, Cyclosporine, Colchicine, Dapsone [Antibiotics]
  3. Photo therapy < PUVA (oral or Scat), Grenz-Zone Ht

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⊙ Acrodermatitis Continua of Hallopeau:
(Dermatitis Repens)

- Chr., sterile, pustular Eruption affect, Initially tips of fingers or Toes
- Unilat / or Bilat Asymm
- start as: Pustules at nail bed / or Paronychia → extension
- ⊇ Recurrent Eruption & exfoliation → : nail dystrophy or Float away or Lakes of pus

- MM: → Geographic Tongue (نادر)

- Fate: usually Remains stable & in Rare Cases → Von Zumbusch ps.

with: Nail bed or Fold pustules + Annulus migrans.. (Paronychia)

- DD: ① Pulp inf.
② Herpetic whitlow.
③ Tinea unguium & paronychia
④ Parakeratosis Pustulosa: form of Eczema dermatitis ⊙ usually seen in Children (Sp. Girls) (< 5 Ys) (Finger Tips)
Affect the skin around the nail & ass. ⊇ subungual Hyperkeratosis thickened free edge & pitting.
In this Condition: Scaling More obv than pustulosis
Cs / Dandruff
Sulfapyridine / PUVA
MT

- DD of: Palmo-plantar eruptions or Pustules
① Pustular bacterid
② PP Pustulosis
③ Acrodermatitis Continua
④ infantile Acro-pustulosis
⑤ Pompholyx (Bul. — No pustules only Vesicles) HH

ex dish

Generalized Pustular Psoriasis
(Von Zumbosch)

Def: Severest form of psoriasis characterised by widespread pustules on an erythematous background due to macroscopic accomulation of neutrophils.

Genetic ↑ HLA ⊠
Immunological ↑ Neut. Chemotaxis.

Pathophysiology (HL)

2- Enhanced polymorphonuclear leukocyte (PMNL) chemotaxis: is much more pronounced in pustular psoriasis than in psoriasis vulgaris.
*cause: either an intrinsic PMNL defect or to the presence of chemoattractants in the psoriatic epidermis. Although the principal stimulus that triggers the phenomenon of massive PMNL migration from the vasculature to the epidermis is unknown, cytokines elaborated by keratinocytes are believed to aid the process.

2- E/M: show basal keratinocyte herniations. These are cytoplasmic processes from basal keratinocytes that protrude into the dermis through gaps in the basal lamina in lesions of pustular psoriasis. These hemiations mostly are clustered over collections of neutrophils in the dermis. This finding suggests an increased production of neutrophilic proteolytic enzymes in the dermis of these patients.

3- Immunohistochemical methods : have determined the involvement of some of these proteases and their inhibitors in the development of pustulation. Elastase is a proteolytic enzyme released by PMNLs during the process of extravasation and migration through the dermoepidermal junction. An epidermal elastase inhibitor, termed skin-derived antileukoproteinase, was found expressed in psoriatic skin prior to influx of PMNLs and to disappear when the composition of the infiltrate changed. This finding was not confirmed by other studies.
4- decreased natural killer cell activity in generalized pustular psoriasis.

4-↑↑ HLA-B27 also has been found among patients with pustular psoriasis (This also is seen in psoriasis patients with peripheral arthritis, as well as in patients with ankylosing spondylitis and reactive arthritis).

**** It may start as:***

1- Pustular psoriasis from the onset (rare) (de novo)
2- As acomplication of ps. Vulgaris under certain provactive factors:

- Idiopathic.
- Infec°.
- Hypocat
- Treatment:
  - Topical: → Irritants (zinc prith & Selsun Blue. Tar anthraline Cs underocclusion.
  - Phototherapy & Photatoxicity
  - Systemic: rapid withdrawal of any systemic

- Pathology: its hallmark is presence of spongiaform pustules of Kogoj ⇒ quickly become Macroscopic.

(agg)

(begin Cs)

CIP:-

1. General Manifs: Abrupt onset of FAHN.
2. Cut. manifs:

- Skin: preexisting skin lesions become fiery red & develop numerous pustules → then → sheets of Erythema & Desquamation start to affect Non Psoriatic areas specially Flexures & Genitalia.

(lesional skin / non lesional)

- MM: Involved ē Geographic Tongue, Pustular & Dysphagia.

- Nails: become thickened & separated by sub-ungual lakes of pus.

- Fate: either
  1. Fatal: d/t exhaustion, Toxicity & Inf.
  1 or 2. Remission occurs in (ds-ws) → regression to either original Typical ps. or change to erythrodermic ps.

- Complications:
  1. death.
  2. Hypoalbuminemia: d/t loss of plasma Proteins in tissues.
  3. oligemia
  4. liver → damage (d/t < digenia & general toxicity)
  5. GIT → Malabsorpt= (Dermatogenic enteropathy)
  6. Resp. → Pulm. Embolism.
  7. Skin → staphi inf.
  8. Hair → loss (TE aft 2-3 m).
  9. Joint → Pol arthritis

INVs
- ↑ ESR
- ↑ WBCs
- ↓ Albumin
- ↓ Cat.

- Mx: 1. Hospitalizat= → Rest, Hydrat=, Hand topical Corticos
  2. Acitretin → of choice. Others → Systemic ill

(1) Generalized pustular psoriasis of pregnancy (Impetigo Herpetiformis)

dx - Special type of pustular PS. that may occur during pregnancy (d.t) high Progesterone level.

Onset - usually start at 3rd trimester (but can occur at any time) & usually persist till delivery;

Recr. - Also may Recur in subsequent pregnancy or OCPs.

Clf - Start as: Flexural Erythema sluded pustules → Generalized pustular flare → Complication
- Toxicity
- HF
- RF
- IUFD

Mx (1.) Termination as safe as possible.

(2.) Retinoids (CI d.t pregnancy)

(3.) Cs: 1 mg/kg/day (Here is indicated while in Chr. plaque PS → CI)

(3.) Annular pattern: (More chronic, less severe):
- Annular, erythematous scaly lesions & pustules at the advancing edge. → Central healing & peripheral expansion.

(4.) Localized pattern: (localized only to PS lesions/NB NL skin affected)
- pustules may develop at the edge (or) within the Existing psoriatic lesions.
- Seen in: < unstable course of chr-plaque PS / Tar use.

(5.) Exanthematic type: (AGEP) - acute Eruption of sterile pustules, abruptly appearing & disappearing
- Mx: Inf. / Lithium
- DD: AGEP

(6) Infantile & Juvenile pustular ps:

- Start in 1st few wks of life.
- has benign course with No constitutional Manifs.

Erythrodermic psoriasis

(also see Erythroderma)

def. ps. involving all or almost all of the Cut. surface.

Etiopathogenesis: may

1. Start as Ivy manif. (rare)
2. Complicate Chr. Plaque or unstable ps. thal-is
   ppt by: inf., Hypo Ca, strong HF by Cs & tar.
3. represent resolving pustular ps.

PPT Factors: (as pustular)
- inf.
- Hypo Ca
- Cs withdrawal
- Tar
- Antimalarial. (Easy)

- Clue For Dx: Facial sparing & nail involvement.

Complications of Erythrodermic ps

Treatment → see Erythroderma

1. HF & myocardial dis.: dt ↑ Blood flow → ↑ Cop.
2. Hypothermia: d.t Cut. VD & ↑ Heat loss
3. Hypo-thermia: Spread duct occlusion.
4. Dermatogenic Enteropathy [Malabs]
5. Hypoproteinemia & Fe deficiency
6. Dehydration: d.t impaired barrier function.
7. Electrolyte Imbalance

Pathology of Psoriasis

- Parakeratosis (focal & alternating with Foci of Orthokeratosis in a Rythmic fashion)
  - "Hyperkeratosis cout parakeratosis"
- Hypogranulosis
- Acanthosis.
- Rete Ridges → (Psoriasiform Hyperplasia)
  - Regular Elongation: Test-Tube like
  - Clubbed (Thickened lower ends)
- Dermal papillae: (earliest feature)
  - Elongated, oedematous & dilated Tortous Capillaries. (Auspitz Sign.)
  - Thinned Epid. above them (Thinned st. Malpighii)

: 2 Neutrophilic accumulations: "إلتهاب"

d.t migrat of Neutrophil, from the dilated Capillaries in Dermal Papillae.

① in st. Corneum: occurs in all cases of Ps. & called "Munro Microabscesses"

② in st. Malpighii (Prickle Layer): occurs only in pustular ps. & called "Spongiform pustules of Kogoj"

"multilocular pustules Surr. by Sponge-like network made of Flattened KCs."

D.D of Microabscesses

(in MF)

① Munro: Ps, SD, Acrodermatitis Continua & Reiter's

② Pautrier: Mononuclear cells + MF cells in St. Malpighii

③ Papillary → Neutrophils: In DH
→ Eosinophils: in B.P

④ Subcorneal → Candida, Impetigo,

⑤ Kogoj: CPS & other

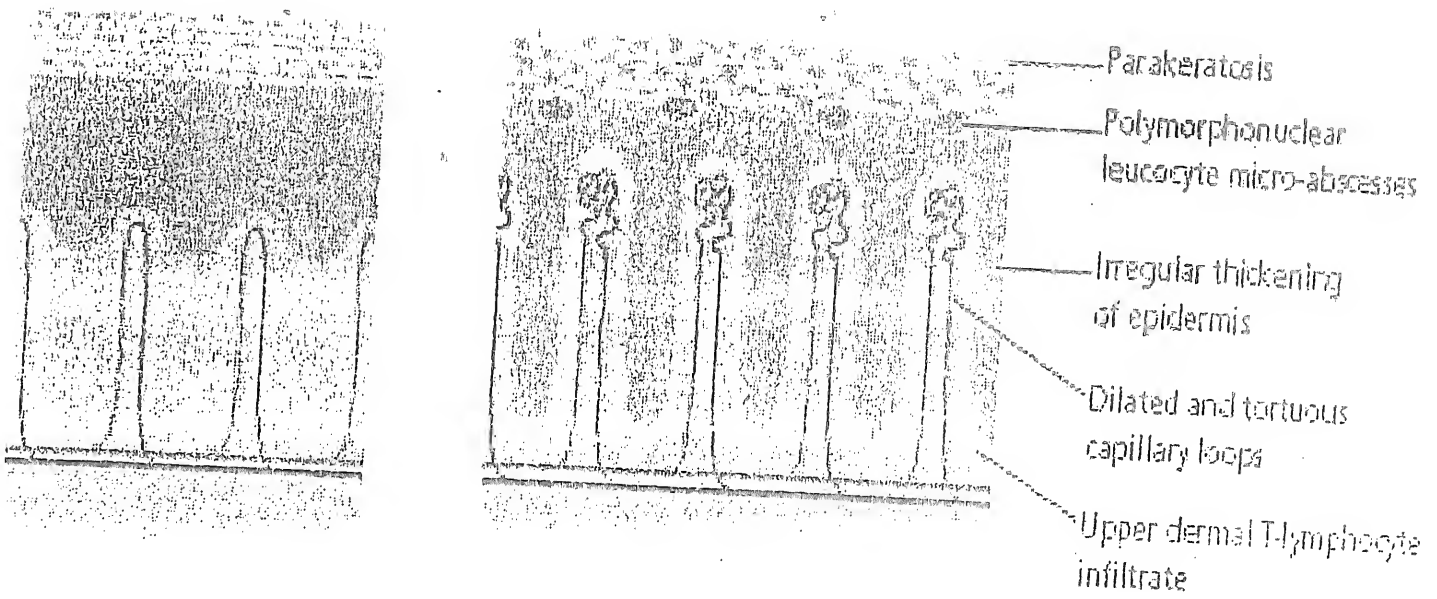


Fig. 5.1 Histology of psoriasis (right) compared with normal skin (left).

Investigations Recently recommended.

- BP Assessment.
- W.t "
- Lipid Profile
- Insulin Resistance (IR)
- ECG.

Metabolic Syndrome.

Ocular Psoriasis

- Ectropion & Trichiosis
- Conjunctivitis & Keratitis
- Corneal dryness & Melt.

Comorbidities.

- Ps Arthritis
- HTN
- Obesity
- CV dis
- DM
- Crohn's
- Liver dis.
- Psychological

Treatment of PS.

(1) General Measures: → to comorbidities ↓ PS. مثال اخرى

- ↓ weight
- stop smoking "مش" & Drugs as ..؟
- Avoid < Stress / Trauma
- Fish oil Dietary supplementation (Max-EPA 30 m/d

(2) Medical therapies:

1. Topical:
   - Cs < Topical ILs.
   - Opt: Calcipotriol, Tazarotene
   - Tar
   - Opt: Anthralin, Salicylic acid 3٪

2. phototherapy:
   - PUVA
   - UVB — NBUVB, Excimer light, Balneotherapy, Climatotherapy.
   - PDT → "photodynamic ؟؟"

3. Systemic therapy:
   - Methotrexate
   - Acitretin
   - Cyclosporine A.
   - Biological therapy.

4. other therapies — Combination: Rotational / Sequential

- Severity تقييم

(i). BSA
(ii). Local ← Limited face.
(iii). Symptoms
(iv). ?? Affected
(v). Physical, Emotional & Functional Impact

Choice of ttt

Psoriasis

- Mild (≤ 2% of BSA) → Topical
- Moderate (3-10% of BSA) → Topical ± / Systemic / Photo
- Severe (>10% of BSA) → Topical ± / Systemic / Photo

Topical ttt

- Indications (1) as a monotherapy in mild to moderate PS.
  (2) as a combination in severe PS.

- Mechanism: (طبي - كيمي - فيزيائي)

"على" any Topical Action or more of the Following mechanism →
1. ↓ KC prolif. (Anti prolif.)
2. ↑ KC maturation (Differentiation)
3. Immunomodulation. (Anti inflammatory)

- Cs, Tar & Anthraline < 1, 3
- Calcipotriol : 3 mechanisms.
- Tazarotene : 1 & 2 in.

- Mild-Mod
  - Month.
  - 1st line < Cl Calcip.
  - 2nd : others
- Severe Ps :

- Topical Eczema (5)
  - Indicat
  - Mech.
  - SE
  - CI
  - How to Use
  - Preg.

Topical Cs < Topical Intra lesional for < Topical Nail Ps:

- Indications: (1.) mild psoriasis: as 1st line monotherapy

(2) Moderate-severe Ps in combination ē other systemic + therapies

(Maxiaff → 3) Face & Flexural Ps (other Topicals are Irritants)

(4) Recalcitrant plaque lesions (used under occlusion (or) ±L.)

- Mechanism (1.) ↓ KC prolif.

(2.) Immunomodulation (↓ inflamm)] by binding To GRE (gluco. Corticoid Response Element).

- Regimen (طريقة الاستعمال)

Start with:
- Potent or Superpotent
  - EoD أو مرتين يوميا
  - مرهم
  - under occlusion تحت

For 2-3 ws
- maximal improvement

then.

Maintenance Therapy
- Use Weekends Therapy
  - [دهان مرتين في الأسبوع]
  - For 12 ws
  - Correc ence.

- NB: (1.) once 1 day is as effective as twice 1 day

(2) Face & Flexures → Hydrocortisone 1 (↓ inflamm. ē out Effect on prolif.).

- S.E: تأثير جانبي
  - Local → (Tachyphylaxis) Lack ē effect after Repeated use
    - To avoid: Weekend H ē Change Type
- C.I: (1.) infection < Bact. Viral fungal
  - (2) Atrophy
  - (3) CD.

Vit. D3 analogues

- Calcipotriol (calcipotriene) = 50 µg/gm
- Maxacalcitol
- Cacitriol (Silkis) → active form of vit D3.
- Tacalcitol (Curaloderm)

- **Indications**: See 1 & 2 in Cs.

Mechanism: (3)

1. ↓ KC prolif.
2. ↑ KC differentiation
3. Immunomodulatory (↑IL10 & ↓IL8)

(++ cornified envelop formation & ++ Transglutaminase)

Hyperprolif. keratins ↓ K6, 16 & 7 (1-2 ws)
↑ K1, 2, 10 (2-3 ws)
↑ IL10 & ↓ IL8
- Immune Suppressive
- antinflamm.
- Inflam. Cyto Kine → ↑ KC prol

- **S.E**:
  1. irritation (in face & Flexures)
  2. with S.A → inactivation of Calcipotriol.
  3. with NB-UVB or PUVA → degraded brit & at same time act as photoprotective so preventing its effect.

(i). irritate
(ii). Dryness
(iii). Combination

(بعد) (بعد) (بعد)

ولذا: لابد من إستخدامه قبل جلسة بفترة أكثر من ساعتين أو بعد الجلسة.

- **C.I**
  1. Pregnant (Category C)
  2. Lactating
  3. > 100 gm/w (أكثر من أنبوبة واحدة/أسبوع)
  4. Renal dysf. (Hypercalcemia may occur) ⇐ dose < 100 gm/w
  5. Hypercalcemia ⇐ abn Ca++ or bone metabolism (Sarcoidosis)
  6. Allergy

How to use (Regimen)

1. as Monotherapy
2. with Cs →
3. ē Photo therapy
4. ē Systemic therapy.

How to use it in psoriasis ??

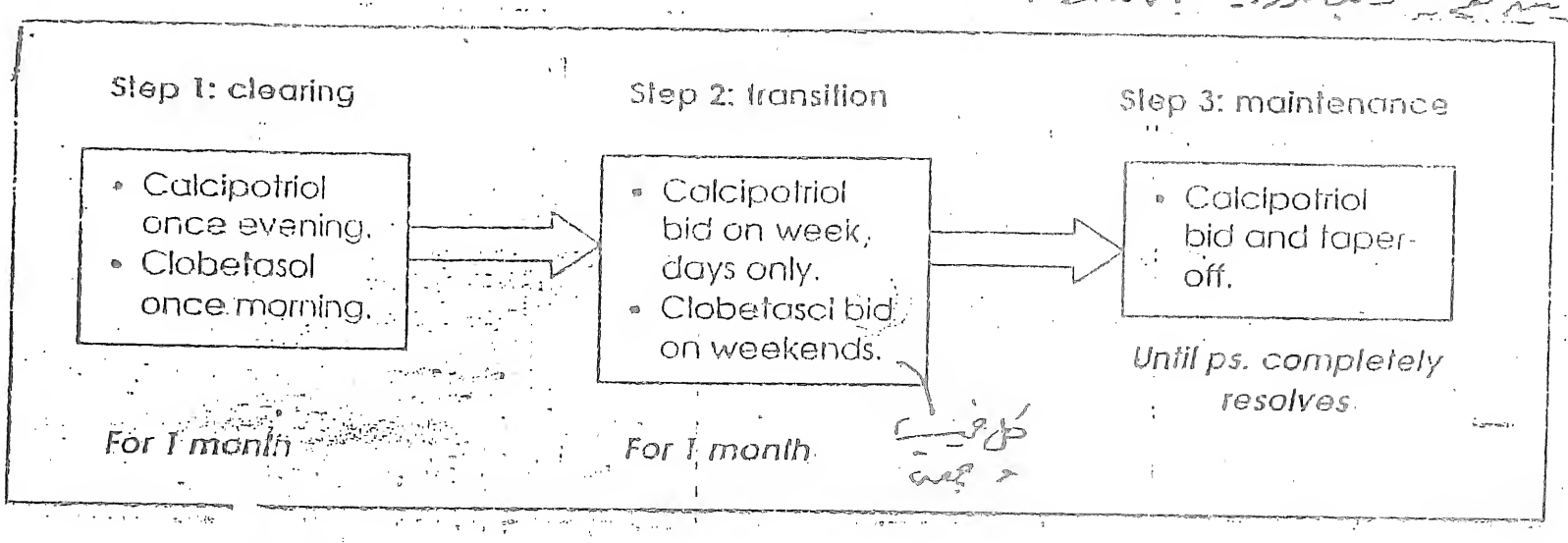
(1.) as a monotherapy : يستخدم كعلاج أحادي

Good in Face & Flexures (to avoid Cs S.E but ± irritant).

(2.) With Cs: "مع"

a. Diavonex مع + Dermovate

b. Sequential therapy: يستخدم بالتتابع
Diav. في البداية + Cs
Diav. في النهاية



c. Pulse therapy: على الـ Daivonex فقط.
(Weekends) في نهاية الأسبوع Dermovate الـ

d. Combination therapy: (Daivobet) ointment
Diav. 50 µg/gm + Betamethasone dipropionate 0.5 mg/gm.

→ rapid onset of action superior to either calcipotriol or betamethasone diproprionate alone. The challenge was to combine a Vit. D3 analogue (works optimally at alkaline pHs) & a corticosteroid (works optimally at acidic pHs) while maintaining stability & achieving optimal bio-availability

+ e. Maintenance therapy: (To Perform long Term Remission) (بعد فترة من العلاج بالكورتيكوزون ولفترة ممكن تصل الى سنة)

NB = may be used under occlusion.

③ with phototherapy (as in vitiligo)

أ) قبل الجلسة بفترة قصيرة بعرضه لمصدر الضوء !!

(why)

Calcipatriol ⟶ photoprotective

Photodegradation ⟵ phototherapy

④ with MTX, Acitretine or CyA: Combined will then to ↓ dose of these drugs & ↓ S.E

جيل تالت Tazarotene (Zarotex gel) ®

- The only Topical Retinoid used in ##ع ps. (all others are not effective).
- Mechanism: binds to Retinoic acid Receptors: RAR-(β & γ)
  - (1.) ↓ KC prolif. (-- glutaminase & K16)
  - (2.) ↑ KC differentiate
  - (3.) Immunomodulation (±)
- Indications: mild PS: as 2nd line of as monotherapy or in Combination in photochemo
- C.I:
  1. Erythrodermic ps.
  2. Progressive unstable ps.
  3. pregnancy & lactation
- SE → ACD. (contact dermatitis) & Teratogenicity

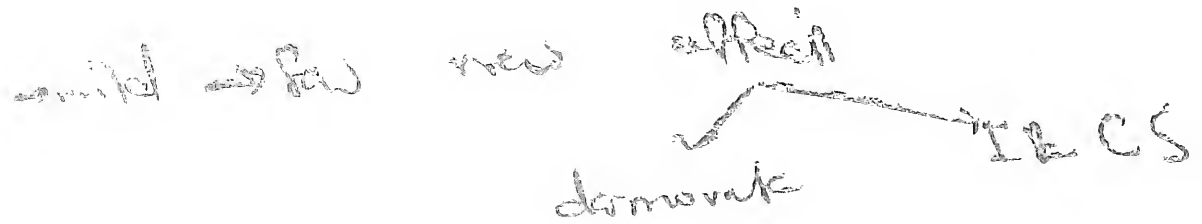
Retinoics ← Pregnancy Category - X (c).

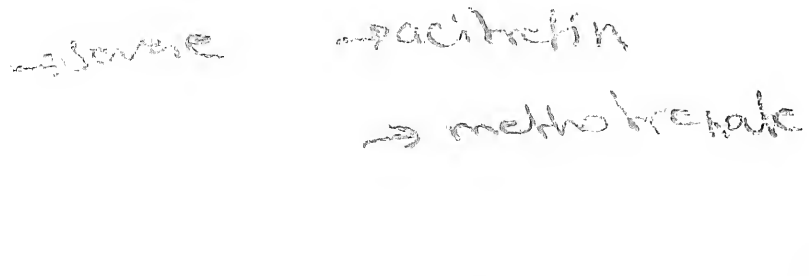
- How to use (Regimen):
  - (1.) alone; but ↑ irritant
  - (2.) with Cs: Betamethasone fluorate (< ↑ efficacy & ↓ irritation)
  - (3.) with UVB (↓ UVB dose by ≃ 1/3 to avoid burning)
  - (4.) with 5-FU: for warts ps. (الثآليل)

?? → Alone, Topical Cs/5FU, phototh.

- Efficacy: moderate (50% improvement in 50% of cases after 6 wks of ##).
- Limitation:
  - BSA: maximum use of it for (10–20%) BSA
  - duration: for upto 1 year.

nail Psoriasis





Tar & Anthraline

Tar (Crude Coal Tar)

- Mech. (1.) Antiproliferative
  (2.) Anti inflammatory
  (3) Antipsoriatic
  (4.) Antimicrobial (Bacterial)

- Use either:
  - Alone as Cs
  - or Goeckerman Technique
    - Tar + UVB (Suberythem)

- Indications: as Anthral

- C-I: as Anthraline + pregnancy (C)

- S.E
  - irritation, staining of clothes
  - bad odour
  - folliculitis
  - Acneiform Eruption

*polytar shampoo
*nice hair plus

كريم يستعمل لفترة 2-1 ساعات ثم يغسل بالماء والشامبو ثم يستعمل المرطب

كريم يستعمل لفترة قصيرة ثم يغسل بالماء والشامبو

Anthraline (Dithranol) (Micranolic®)

Mechanism (1.) ↓ KC Prolif.
(2.) Immunomodulation:
- -- Neutrophil Chemotaxis
- ↓ IL1 & 6.

Use: either:
- Ingram Technique (od's) or
- Short Contact therapy (to ↓ S.

: Tar (bath) + UVB
Then → Anthralin (Twice daily in Lassars Paste; S.A, Zinc oxide, + Paraffin).

: light for (زيادة التركيز بالتدريج) 5-30 min. then Washed (غسيل)

غير لبنتر

غير لبنتر

Indications: mild to moderate or Severe Psoriasis:
2nd line tt as mono. therapy or in combinat.

C-I
1. Pustular ps
2. Erythrodermic ps.
3. Progressive unstable Ps.
4. Hypersensitivity / Excoriated skin.

S.E: irritant & staining
- Clothes
- Skin (Purple-brown)

Efficacy: Very effective

Pregnancy: Category C

"Scalp Ps.

Callomac → SA 16.7% Other Topicals

- Salicylic acid
- 5. FU
- Calcineurin inhibitors (for Face & Flexural Ps)

لذا الكريم → . Moisturizers

* Salicylic acid *

. . Mech. (1) Keratolytic — فقر C

↓

-- Cholesterol sulfotransferase

↓ cholesterol sulfate formation

↓

Solubilization of intra Cellular Cement substance

↓

Loss of Cellular Adhesion

↓

Keratolysis.

(2) Mild Anti-inflammatory

(3) bacteriostatic & Fungistatic

↓

by -- eg panthoenic acid.

. Concentration: 0.5% — 40%

< 5% → keratolytic

scaling dis. → 1-5%

Part : 10 - 40%

. S.E (depend on Conc. & Surface area & application)

(1) irritation, Erosion, Ulcerate

(2) Systemic absorption (Salicylism)

Specially infants & newborn

→ Neurological & GIT Toxicity.

(3) Pregnancy (Category C) : may

Cause Premature Closure of ductus arteriosus → pulm HTN

(C when used in late pregnancy).

---

5 FU (0.5 - 5%) : -- enz: thymidylate Synthetase → -- DNA Synth.

. Treatment of wart. Ps.

كريمة نحاله ← : 1% - 5 FU + Tazarotene 0.1% (مع تعريض)

بعرض ، ٤ - eludex - ecrolex

Phototherapy

Indications: → Mod. - severe Ps.

① Ps. vulgaris affecting ≥ 3-10% of BSA as 1st line Month ± in Combination ± Topicals.

② When systemic therapy is C.I ✓

A. PUVA [unknown Mech.] ← Antiprolif. Anti inflamm.

① Antiprolif. (by -- DNA replicat~)

② affect cytokines release.

B. NBUVB [unknown ?]: ← anti anti inflamm

(أهم سؤال) → ① Antiprolif. (-- DNA replicat~ by formate of Pyrimidine dimers] → -- Cellular prolif.

② ↑ PGs

③ ↓ ILs: (12), 18, (23) & ↓ Th17.

④ ↓ NK cells

⑤ -- APCs.

(مجاله)

C- BALNEOPHOTOTHERAPY (Dead Sea therapy): Empirically, it has been known that the combination of salt-water bathing and sunlight exposure is an effective treatment for psoriasis. From studies at the Dead Sea, it became clear that highly concentrated salt water (>20%) together with UVB light is most effective.65 This therapeutic strategy also was termed balneophototherapy; it has become increasingly popular in Europe, where concentrated salt-water baths together with artificial UVB sources are used in psoriasis treatment centers. A possible mechanism of concentrated salt-water bathing is the elution of biologically active peptide mediators and enzymes such as human leukocyte elastase from the inflamed skin.

D- Heliotherapy (also called climatotherapy): makes simple use of intentional direct exposure to natural sunlight to get the therapeutic benefits of the included ultraviolet radiation. The use of heliotherapy began a long time ago when it was used in India, China and Egypt to treat diseases, including psoriasis. Ancient Greeks also used natural sunlight as therapy. As far back as 3,000 years, medical practitioners were advanced enough to use sunlight-sensitizing chemicals before sun exposure - a primitive version of today's photochemotherapy or PUVA. Heliotherapy has been studied, and it works. Benefits lasting beyond a year have even been documented.

Systemic Therapy

Indications:

IF

- Ps. is moderate-severe: defined as:
  - Psoriasis vulgaris ≥ 3-10% BSA or
  - Pustular psoriasis (Generalized or Localized)
  - Erythrodermic Ps.
  - Psoriatic arthritis (mod-severe)
  - Severe nail ps.

"Interfere Psocial behav. & Emo. me.

- Photo therapy is:
  - C.I
  - Failed (Resistant)
  - Inapropriate (Ps. Arthritis & Nail) also - pustular / Eryth

So if Ps. is: Moderate-severe → Phototherapy

If: C.I / Failed / Inapropriate
- nail Ps
- Ps. Arthropath

Phototherapy → if: Failed / C.I → Systemic therapy (MTX, Acit. & Ciclosp) → Biological Therapy

The treatment must not be worse than the disease.
"Side effects are often the limiting factor in psoriasis treatment"

Systemic steroids are condemned in psoriasis.

Methotrexate (Amethopterin)

- Introduction, Basic & Mechanism:

• Folic acid (vit M) & Folate (amonic form) are Forms of vit: Bc.

- Metabolism: (① Folate → ② DiH. folate → ③ Tetra H. F. → Purine)

Folic acid (Folate) —Reduced To→ Dihydrofolate (DHF)

Reduced by enz. DHFR (dihydrofolate reductase)

Tetrahydrofolate (THF)

Thymidylate Synthetase enz.

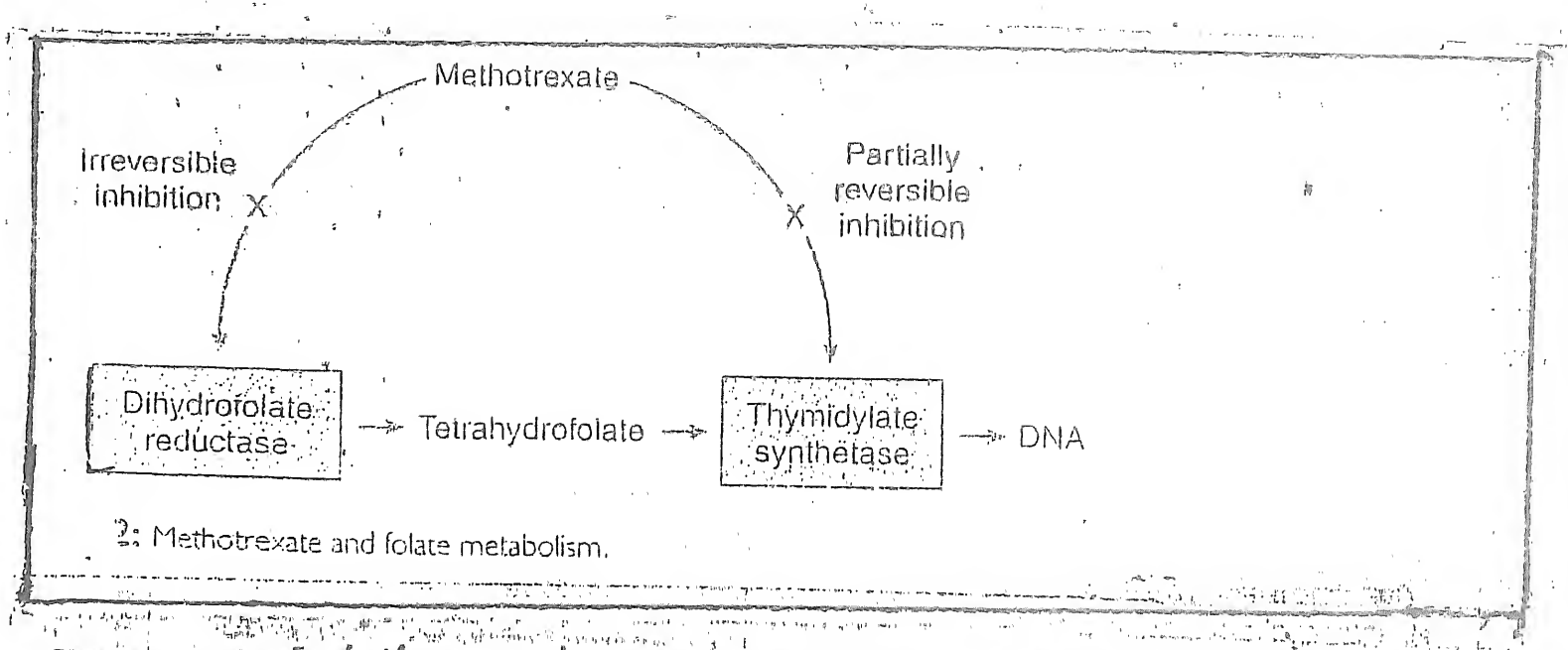
Purines

Thymidylate

-- 2 enz. Yes
① DHFR → Complete irreversible
② Thymidylate Synthetase → Partial irreversible.

-- DNA & RNA Synth.

• DNA & RNA Synth (So → -- cell division during S phase)



2: Methotrexate and folate metabolism.

This Inhibition is Competitive because Structure of MTX similar to DHF but it very higher affinity to the DHFR enz.

• This inhibitory effect is very Marked on highly dividing cells (BG, Lymphoid cells, BM cell & Mg cells).

- Mechanism of Action: (MTX) ← Antiprolif by -- KC prolif.
  Immunos. by -- Lymph. ↓
  Antiinflamm. by -- SAM.

① Antiproliferative (in large doses for Cancer Rx):

.-- of Cellular prolif. (KCs, Lymphocytes, B-M Cells & Mgs Cells).

Through: inhibition of 2 enzymes ← DHFR & Thymidylate Synthetase

ps. ← کاردیتقد انہ دہ میکانیزمہ ئ ps. دەبێ تاثیرەکەی وەکو --KC prolif. وەکو ئەبێ TCells ی ... بۆ KCs

② Immunosuppressive: (In Psoriasis)

میکانیزمی ps ٢ ← ١

.-- Lymphocyte prolif. (Long Time Point > Effect on Lymph. on K Trafficking..

.-- "

. ↓ Neut. chemotaxis.

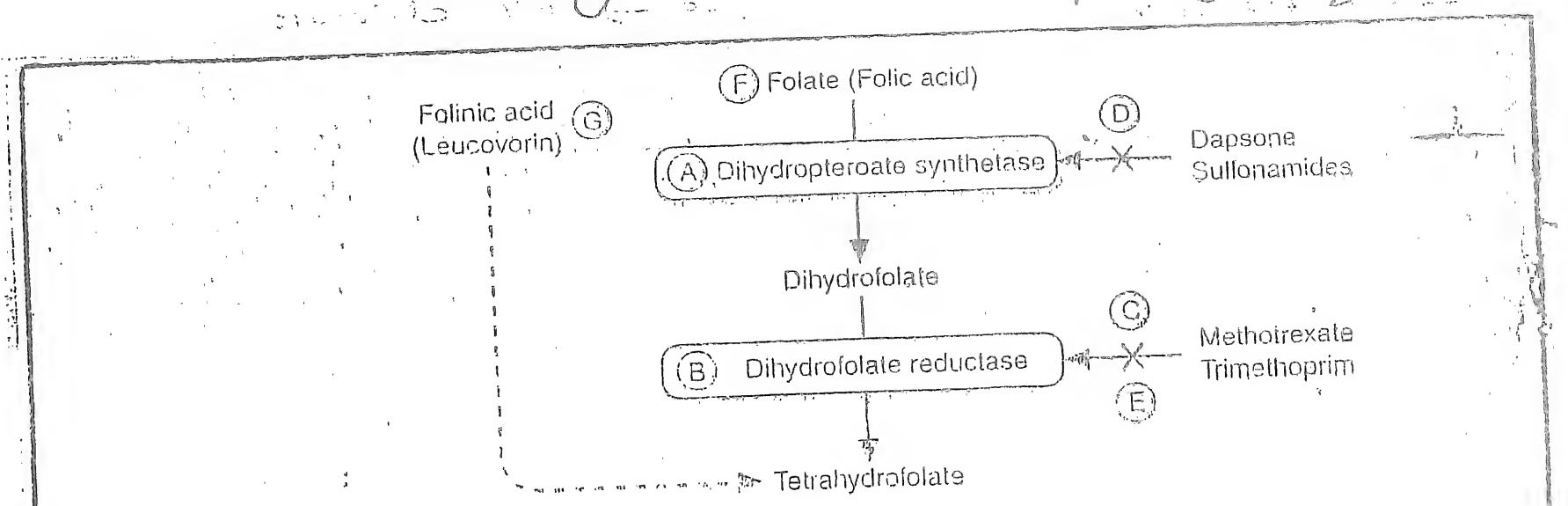
. ↓ Histamine release.

③ Anti-inflamatory:

: ↓ SAM (S adenosyl methionine) → ↑ Add

→ ↓ inflamm.

: through its Immunosuppressing Effect.



* In general, this metabolic pathway is more important to the adverse effects of methotrexate (including drug interactions) than it is for drug efficacy. The fully reduced tetrahydrofolate is important for subsequent pyrimidine nucleotide synthesis.

A Folate (folic acid) is initially reduced to dihydrofolate by dihydropteroate synthetase.

B Dihydrofolate if further reduced to tetrahydrofolate by dihydrofolate reductase.

C Methotrexate inhibits this pathway through competitive inhibition of dihydrofolate reductase (DHFR).

D Dapsone and various sulfonamides inhibit dihydropteroate synthetase, and thus, can amplify the inhibition of DHFR by methotrexate.

E Trimethoprim (including fixed combinations with sulfamethoxazole) also inhibits DHFR, and thus can amplify the inhibition of this pathway by methotrexate.

F Folic acid given in therapeutic doses essentially competes with methotrexate for DHFR, ↓ the adverse effects of methotrexate by ↑ tetrahydrofolate production.

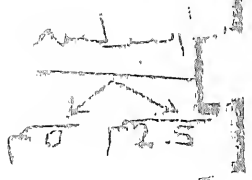
G Folinic acid, in a sense does an "end run" around the methotrexate inhibition of folate, serving as a fully reduced substrate for pyrimidine synthesis.

Figure 8-3: Methotrexate and folate metabolism, drug interactions of importance.

MTX:
لا تبطى
يوميا

Dosage & Administration:

- Preparations:
  - MTX tab. 2.5 mg.
  - MTX injection: (50 mg lampul)
- Routes: oral, IM, IV & (Topical)
- Doses:
  - 5 - 30 mg/w
  - Psoriasis usually improve @ 15-25 mg/w
  - usually don't exceed 80 mg/w.
- in children: 0.2 - 0.4 mg/kg/w.



- Method:

[Doses < 20] → Oral (Triple week schedule)

given as:

3 divided doses (5 mg)

at 12 hrs apart / week.

(8 am → 8 pm → 8 am)

Parentral

IM or IV

- Indications: < GIT ↓ Abs.
  - ① If the oral dose needed to be > 20 mg/w

(at this dose → absorption is poor)

  - ② Erythroderma: d.t malabsorption.
  - ③ Severe GIT Symptoms

- NB. Med Week schedule is Toxic (Not used [تعطى جرعة كبيرة])

E

(I. Regimen)

(خامس الفصل)

PreTH invs are NL

→ Start with Test dose 5mg

(To avoid Idiosyncratic pancytopenia)

(إعطاء جرعة)

بعد أسبوع من الجرعة ↓

Repeat
- CBC "مهم"
- Liver
- Kidney

(BM is highly active and abnormals as pancytopenia may appear after 7 days)

if No detected Abnormalities

: علاج

Folic acid 1-5 mg/day

(مع عدا يتم مع MTX)

or

give folic acid 5-7 mg/w (AAFP 2000)

Why ??

1. ↓ GIT upset
2. ↓ Blood complicat^ (Pancytopenia)

Note: Efficacy

onset 2-6 ws — Maximum 12 w.

give 7.5 mg/w → gradually ↑↑ the dose by 2.5 mg/w (depending upon efficacy & (S.E))

(usually at 10-25 mg/w)

Results:

Good response then maintained for 1-2 ms → gradual tapering by 2.5 mg/w

(لكن ما نوصل لأقل جرعة متحملة إلها)

Bad response → ↑ the dose gradually by 2.5 mg/w (Max 30 mg/w)

NB: (if you on oral & dose needed is > 20 mg/w → (Shift from oral to IM or IV)

Indications, C-I, S.E, Monitoring Guidelines

Box 8-1: Methotrexate Indications and Contraindications

FDA-approved dermatologic indications

Psoriasis[16]
Sezary syndrome[17,66]

Off-label dermatologic uses

Proliferative dermatoses
Pityriasis rubra pilaris[25–27]
Pityriasis lichenoides et varioliformis acuta[28,62]
Reiter's disease[29]

Immunobullous dermatoses
Pemphigus vulgaris[30,31]
Bullous pemphigoid[31–34]
Cicatricial pemphigoid[35]
Epidermolysis bullosa acquisita[36]

Autoimmune connective tissue diseases
Dermatomyositis[37–41]
Subacute cutaneous lupus erythematosus[42]
Systemic lupus erythematosus[43]
Systemic scleroderma[44]
Morphea/localized scleroderma[45–47]

Vasculitis and neutrophilic dermatoses
Leukocytoclastic vasculitis[48]
Cutaneous polyarteritis nodosa[49,50]
Behçet's disease[50]
Kawasaki disease[51]
Pyoderma gangrenosum[52,53]

Dermatitis
Atopic dermatitis[54,55]

Other dermatoses
Sarcoidosis[56–60]
Keloids[61]
Lymphomatoid papulosis[62]
Keratoacanthomas (intralesional)[63]
Mycosis fungoides[65,66]
Cutaneous Crohn's disease[67,68]
Chronic idiopathic urticaria[69]

Contraindications[19]

Absolute
Pregnancy (X) → بالنسبة للحمل → ♀ → ممنوع أثناء الحمل وقبله ٦ شهور بعد وقفه
♂ → يستعمل العازل لمدة ٣ شهور (T.Teratogen)
Lactation

Relative
- CBC: Severe Impairment.
- Liver: disturbed enzs, Active hepatitis, Cirrhosis, Hx of live dis.
- Renal: Impairment (C.clearance <60 ml/min) (↓ dose)
- Others:
  - Alcoholics
  - D.M
  - Obesity
  → High risk For Complicat.
- Immunodeficiency (HIV)
- Inf. → Active inf. or Hx. of Serious inf. (Hep B, TB.)
- Active PSL.

Pregnancy Category: "X"

- S.E of Methotrexate:-

Most frequent[71]	① Subjective.
Nausea	
Vomiting	
Abdominal pain	
Fatigue	
Headache	
Occasional	
Dizziness	
Loss of libido	
Impaired memory	

② CBC: Pancytopenia.
③ Liver: Hepatitis & Cirrhosis.
④ Lung: pneumonitis (Acute onset cough & dyspnea).
⑤ Mucocut (Skin):
- Alopecia
- Photosensitivity
- oral ulcers
- Tenderness / Necrosis of plaque.

Others (Vas): Urticaria & Angiced, Vasculitis.

⑥. Preg. & Lactat:

- Abort
- Teratogenicity
- G.R.
- Cancer.
- Immunosupp.

⑦. Idiosyncrasy [Early in the course & low full dose / بداية العلاج بجرعة قليلة Test dose]

- Pancytopenia
- pneumonia
- GIT Hge.

⑧. Carcinogenesis:

- SCC in PUVA pt ??
- Lymphoma (in RA pt).

⑨. opportunistic Inf:

- Pneumocystis Jirovecia
- Cryptococcosis.

- Risk of Pancytopenia:
  - Early Full dose.
  - No folate.
  - Elderly
  - Renal
  - Interact e: (NSAIDs, Sulfa, Dapsone)
  - DISH
  - Low albumin
  - Ast: 4 wks.

• Monitoring Guidelines:

• Baseline = pre Rx (قبل العلاج)

CBC, Liver, Renal: [1] (قبل العلاج)

- Liver:
  - SGOT
  - SGPT
  - Viruses
  - Albumin. (↓ → ↑ risk of Lung Complic & Toxicity)
- Renal:
  - BUN
  - S. Creatinine
  - Clearance. [2] (قبل العلاج)

- CXR → if previous Hx of chest dis.
- Preg. Test → if in child bearing period
- HIV test: → in risky pt. (Homosex.)

Follow-up (أثناء العلاج)

- CBC: (مرة كل أسبوعين لمدة شهرين ثم مرة كل شهر)
- Liver: (مرة كل شهر)
- Renal: (مرة كل ثلاثة أشهر)

Liver Biopsy → (IF)

- After every 1.5–2.0 g total dose for low-risk patients
- After every 1.0 g total dose for higher-risk patients
- Every 5 months for patients with grade III/IV liver biopsy changes

(بعد كم؟)

- Alcoholics
- Diabetics
- obese
- Hepatitis (HCV, HBV) → non active
- Hx of Liver dis.
- Hepatotoxic Drug.
- Hx of familial liver dis.

(FITZPATRICK)

Classification of Histologic findings in liver Biopsy (of MTX pt)

Grade	Histologic findings:
I	NL liver
II	any of the following: fatty liver. / nuclear variability / Portal tract: Expansion / inflamm. & Necrosis.
III A	Mild fibrosis. (Fibrotic septae extend to lobule)
III B	Mod. – severe fibrosis
IV	Cirrhosis

What's your decision ??

- Grade: I, II → Continue MT.
- III A → Repeat Biopsy in 6 m.
- III B & IV → Stop MT.

هل ممكن نستغني عن ال Biopsy بتحليل آخر؟؟

Yes by Repeated assessment of Amino terminal Pro Collagen III

Drug interactions with MTX:

يجب إعطاء هذه الأدوية بحذر مع المريض على MTX

- NSAIDs
- Trimethoprim
- Sulfonamides
- Dapsone

Also TMP+SMX → ↑↑ DHFR → Additive toxicity

Table 8–2: Drug Interactions—Methotrexate

Interacting drug group	Examples and comments
These drugs may ↑ methotrexate serum levels (and potential toxicity)—displacement from plasma protein	
Antibacterial—other	Chloramphenicol
Antibacterial—tetracyclines	Doxycycline, minocycline, tetracycline
Anticonvulsants	Phenytoin
Antipsychotic agents	Phenothiazines (various)
These drugs may ↑ methotrexate serum levels—↓ renal excretion *and* displacement from plasma proteins	
Antibacterial—sulfonamides	Sulfamethoxazole, others (including TMP/SMX combination)
Anti-inflammatory drugs—other	Salicylates
NSAID (including COX-2)	Various; different NSAID with varying ↓ methotrexate renal excretion
These drugs may ↓ methotrexate serum (or intracellular) levels—other mechanisms	
Antibacterial	Ciprofloxacin, penicillins
Antiplatelet drugs	Dipyridamole; ↑ intracellular accumulation of MTX
Miscellaneous drugs	Amiodarone (mechanism unknown), probenecid; ↑ intracellular accumulation of MTX, also competes with methotrexate for renal tubular secretion
Methotrexate may ↑ serum levels (and potential toxicity) of these drugs	
Bronchodilators—xanthines	Theophylline
Methotrexate may ↓ serum levels of these drugs (loss of efficacy)	
Cardiac drugs—inotropic	Digoxin
Pharmacodynamic interactions—drugs that inhibit these enzymes markedly ↑ risk of hematologic toxicity	
Dihydropteroate synthetase	Dapsone, sulfonamides (notably sulfamethoxazole in TMP/SMX combination)
Dihydrofolate reductase	Trimethoprim, trimetrexate; inhibit same enzyme as methotrexate
Pharmacodynamic interactions, additive effects—drugs with inherent risk for hematologic toxicity	
Antiviral agents	Cidofovir, interferons, zidovudine
Immunosuppressive agents	Azathioprine (see below)
Other drugs with similar effect	Chemotherapeutic agents, clozapine, lamotrigine, etc.
Pharmacodynamic interactions, additive effect—↑ risk of hepatotoxicity	
"Alternative" medical therapies	Black cohosh, kava
Habits	Alcohol (excessive)
Retinoids—systemic	Acitretin, bexarotene
Other interactions of potential importance involving methotrexate	
Antibacterial—other	Aminoglycosides; may ↑ anti-tumor effects of methotrexate
Immunosuppressive agents	Alefacept, azathioprine, corticosteroids, cyclosporine, efalizumab, leflunomide, mycophenolate mofetil, sirolimus, tacrolimus; may ↑ opportunistic infections
Nutritional supplements	Folinic acid (Leucovorin); combined use may ↓ methotrexate efficacy (generally considered that folic acid does not have this same inhibitory effect)

MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drugs; TMP/SMX, trimethoprim/sulfamethoxazole.

Adapted from Facts & Comparisons, The Medical Letter Drug Interactions Program, e-D[illegible]—references on pg. xvii at the Preface.

Over dosage

(Methotrexate Toxicity)

- MTx Toxicity may occurs in the following conditions:

  1. ↓ renal Function.
  2. daily Ingestion..
  3. Concomitant use of Folate antagonist as TMP+SMX ✓

- Treatment → 1. folinic acid Supplementation

  (Leucovorin) (Fully reduced, functional Folate Coenzyme)

  Conversion TO THR directly without need for DHFR Enzyme.

  2. Thymidine: if given it will be converted to thymidylate under effect of Thymidine Kinase enz. without need for Thymidylate Synthetase enz.

HL

- Dose: Start Immediately with 20mg/m² (10mg/m²) either oral or IV & assess MTx level / 18-24 hrs.

MTx level	Leucovorin
0.5×10^{-6} M	20 mg / 6 hr
1×10^{-5} M	100 mg / 6 hr
0.2×10^{-5}	200 mg / 6 hr.

Acitretin in Ps

- 2nd generation Retinoids (Monoaromatic) → Etretinate ✓ / Acitretin

- Mechanism
  1. ↓ KC prolif.
  2. ↑ KC differentiation (Maturation)
  3. Immunological & Anti-inflammatory

- Dose & Administration:
  - dose: 0.5–1 mg/kg/d.
  - In Ps: usually start ē 10–25 mg/day & ↑ gradually to avoid Flare of Ps. at start of Tt

- Indications: as MTX (but Acitretin is the Tt of choice for Pustular Ps)

- Pre Tt Screening: (Ps) (5)
  - Liver function
  - Kidney "
  - Lipid profile
  - Glucose (FBS)
  - pregnancy test "أهم واهم"
  - Spinal XRay (DISH) (لما توقعت انه الالتهاب هايبتد لفترة طويلة / نعمله في أول ٢ سنة)

- During Tt Monitoring:
  - Liver & Lipid profile → كل شهرين لمدة ٦ شهور / ثم كل ٣ شهور
  - Kidney: (For Elderly & those ē mild to med. dysf.)
  - Hyperostosis: → Hx / → XRay: مرة كل سنة
  - pregnancy test " قبل ما تبدأ العلاج

· S.E & C.I → See Therapy

Re-PUVA = Retinoid PUVA

PUVA ↓ ← استخدام الريتينويد

Administration: as

- Mono-therapy
- + PUVA [RePUVA]

✓ Effective > PUVA alone or RCT.
✓ ↓ PUVA dose & Cancer.
∴ ↓ Aging caused by PUVA

·NB:

· صل تكثر نطي ..

Isotretinoin (Neotek)

IS Acitretin واحد تابع نطية بدل سم .

·DISH: Diffuse Idiopathic Skeletal Hyperostosis

·Def Type of degenerative arthritis.

·CF By: Bony, Tendons & ligaments Calcification

·C/P: Pain & Stiffness of Neck & Back.

·X-R: Calcification & (±) Bony Spurs

CYCLOSPORINE

Introduction: Cyclosporine, a cyclic peptide of 11 amino acids, was isolated from the soil fungus *Tolypocladium inflatum Gams* in 1970 and was found to have clinical immunosuppressive effects in 1976. In 1979, during a rheumatoid arthritis trial, it was discovered that cyclosporine improved cutaneous psoriasis in patients with psoriatic arthritis.

Two forms are available:

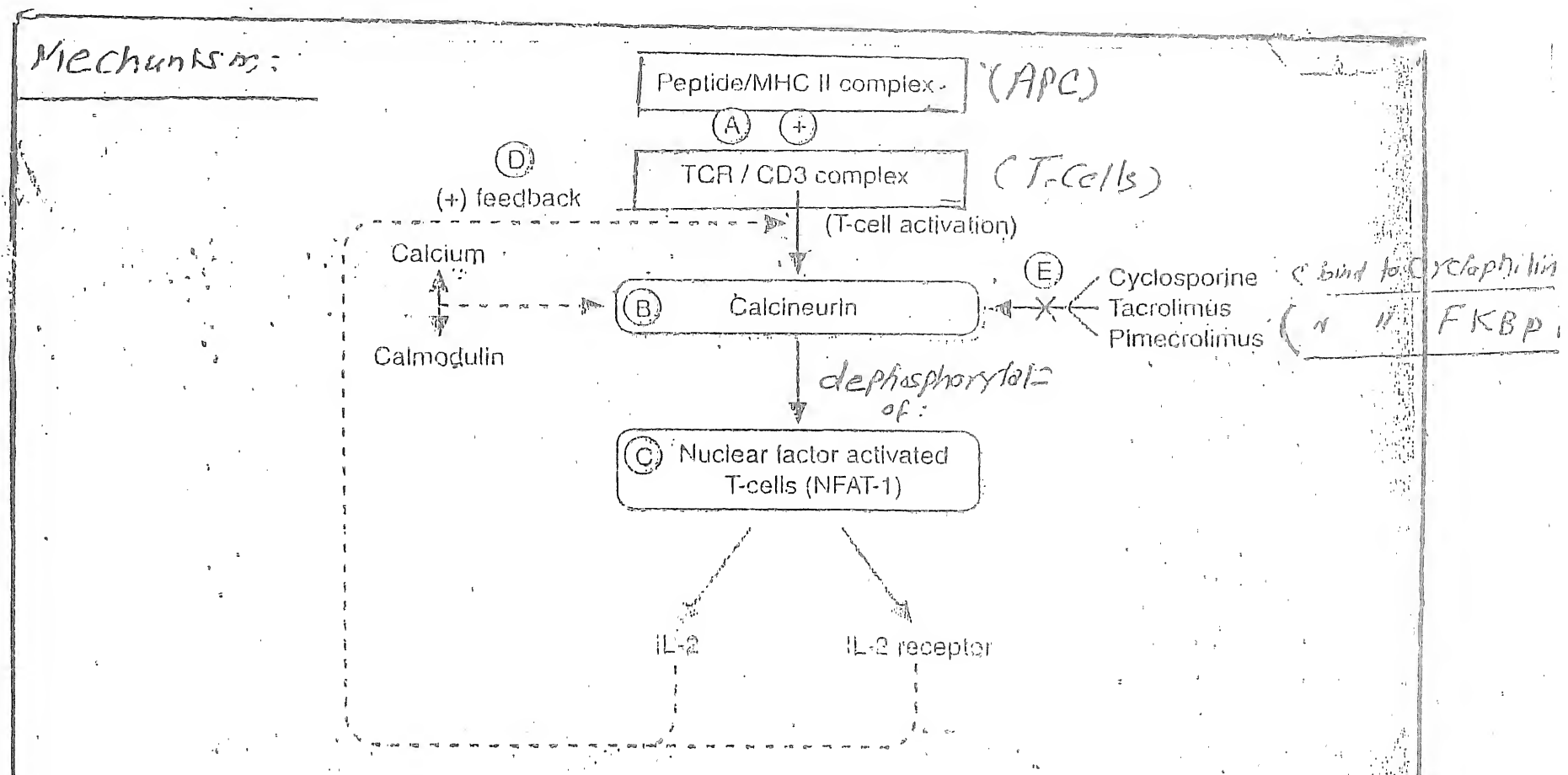
1- (Sandimmune®): 20 and 100 mg Caps.

2- (Neoral®): Predigested microemulsion that is more completely and consistently absorbed: (25 mg, 100 mg) or as an oral solution (100 mg/ml)[12]. The solution can be mixed in orange juice or apple juice, but grapefruit juice should be avoided because it alters cyclosporine's metabolism (see Ch. 131).

Pharmacokinetics:

* Metabolism: by the CYP 3A4 pathway,

* Excretion: is via bile and feces (Only 6% of cyclosporine is excreted unchanged in the urine)



* This calcineurin/"signal 1" system creates a highly efficient immunologic response to various antigenic (or superantigen) stimuli.
A The peptide/MHC II complex on the antigen presenting cell interacts with the T-cell receptor (TCR)/CD3 complex and results in T-cell activation; ↑ calcineurin activity is one result of this T-cell activation.
B With calcium as a cofactor, and through interaction with the calcium binding protein calmodulin, calcineurin ↑ activity of the transcription factor NFAT-1.
C NFAT-1 ↑ formation of both the cytokine IL-2 and the IL-2 receptor.
D Through subsequent binding of IL-2 to IL-2 receptor, the T-cell activation is further amplified.
E Cyclosporine (as well as tacrolimus and pimecrolimus) inhibits the key enzyme, calcineurin, in this system with ↓ IL-2 and ↓ IL-2 receptor production, with the net effect of inhibiting "signal 1".

• Mechanism: (on T-Cells)

(1) Binds to cyclophillin Rs → ↓ Calcineurin protein → ↓ IL-2 production ↓↓ IL-2 Rs Expression → ↓ T cell prolif.

(2) ↓ IFN-γ production → ↓ ICA-M 1 Expression → "↓ T-cell Trafficking."

(3) Binds to steroid Rs ass. ↓ heat shock protein 56 → ↓ IL-1, 4, 5, 6, 10, TNF-α.

• Indications: (CCE) دوك

Box 11-1: Cyclosporine Indications and Contraindications

US FDA-approved indications: - Psoriasis if: شرط

1. Severe psoriasis
2. Recalcitrant, treatment-resistant psoriasis
3. Disabling psoriasis (including localized versions such as hand-and-foot psoriasis)
4. Major life events

Approved indications in other countries*

Psoriasis
Atopic dermatitis[5–8]

Off-label dermatologic uses

Papulosquamous dermatoses
Lichen planus[9–13]

Bullous dermatoses
Pemphigus[14–18]
Pemphigoid[19–22]
Epidermolysis bullosa acquisita[23]
Linear IgA bullous dermatosis[24]

Autoimmune connective tissue diseases
Dermatomyositis[25–27]
Lupus erythematosus[28]
Scleroderma[29–32]

Neutrophilic dermatoses
Behçet's disease[33]
Pyoderma gangrenosum[13–16]

Neoplastic
Sézary's syndrome
Mycosis fungoides

Dermatitis
Atopic dermatitis[5–8]

Alopecia
Alopecia areata[37]
Lichen planopilaris[38]

Granulomatous dermatoses
Granuloma annulare[39–41]
Sarcoidosis[42]

Disorders of keratinization
Pityriasis rubra pilaris[43,44]

Photosensitivity dermatoses
Chronic actinic dermatitis[45]

Other dermatoses
Eosinophilic cellulitis[46]
Kimura's disease[47]
Morphea[48]
Prurigo nodularis[49]
Papular erythroderma of Ofuji[50]
Persistent papular acantholytic dermatosis[51]
Purpura pigmentosa chronica[52]
Reiter's syndrome[53]
Scleromyxedema[54]

Urticaria
Chronic urticaria[55–57]
Cold urticaria[58]
Solar urticaria[59]

Contraindications

- uncontrolled HTN ↓
- Renal impairment
- liver ↓
- phototherapy (↑risk of Cancer)
- Mg (Past or present Hx)
- pregnancy
- Lactat
- Malabs.
- Active Inf.
- Drug interact

Pregnancy prescribing status—category C

* Australia and European Union.

FS: Severe Recalcit Disabling Major life.
AD

• Dosage & Administration:

• Administration: CsA may be used as:

1. Monotherapy. (أحادي)
2. Sequential therapy
3. Rotational therapy. →

---

(1) As a Monotherapy: (2-5-5 mg/kg/d) بداية

• Dosage: (جرعة) (2.5-5 mg/kg/d)

Moderate PS: 2.5 mg/kg/d → ↑ gradually (by) (0.5 mg/kg/d) Every other week till either.

- → Satisfactory Response
- → Maximum dose Reached 5 mg/kg/d.

Severe PS:

(if) start ← maximum dose: 5 mg/kg/d.
→ improvement → Taper by 0.5 mg/kg/d every (EOW) 2ws till minimum effective maintenance dose is Reached.

(2) Sequential therapy: CyA → improvement → Add Acit. or MTX & Tapper CyA by ≃ 1 mg/kg/d → Maintain Acit. or Re-UVA.

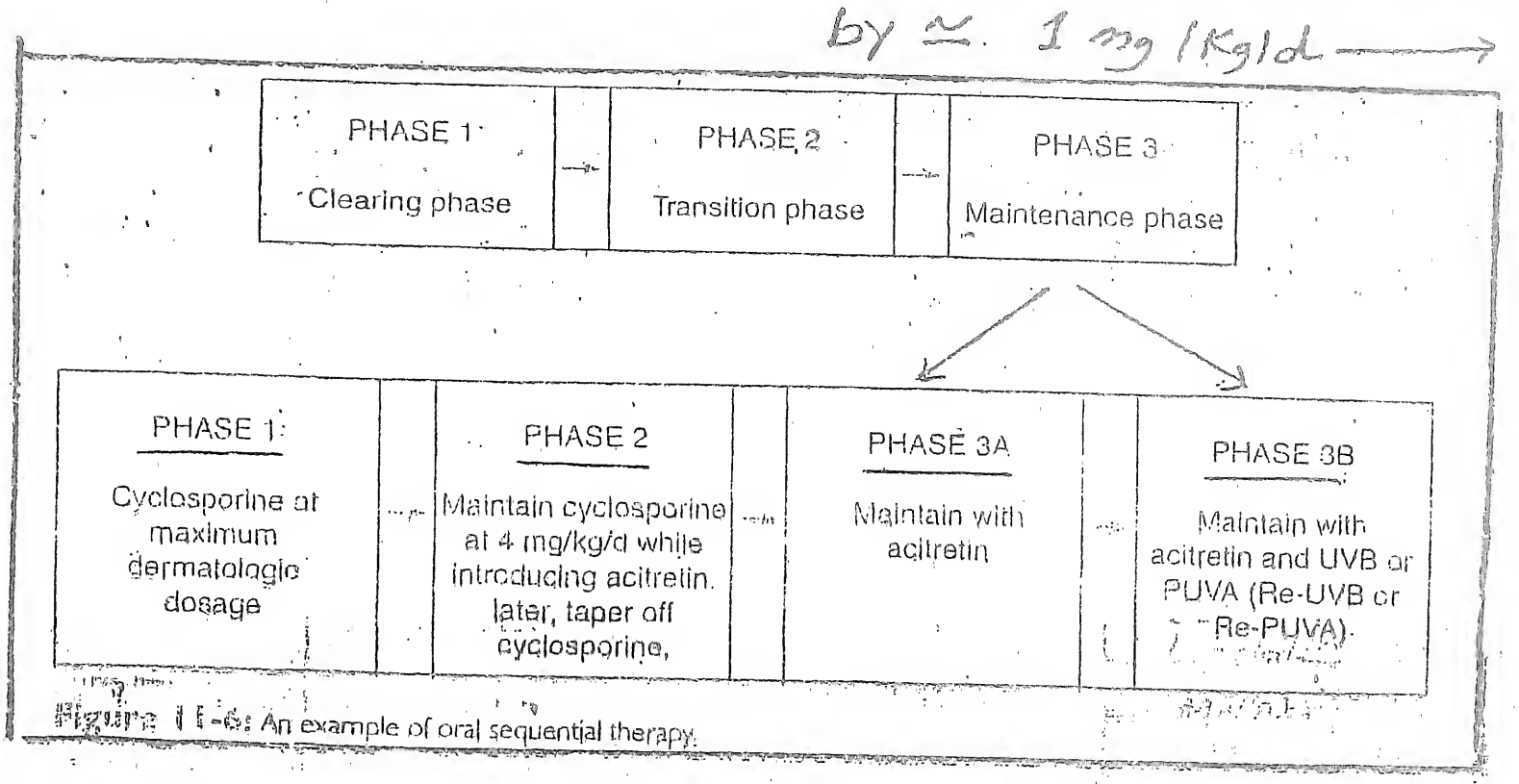


Figure 11-6: An example of oral sequential therapy.

(3) Rotational therapy → see below. (بعدين)

S.E:

① The most important:

- HTN (25% , reversible)
- Nephrotoxicity (sr. > 2 yrs)

2 Hyper - Hypertrichosis & Hyperplasia of Gums.

- Mg (SCC, lymphoma) → (So) not used ∴ phototherapy
- Electrolytes. (3 Hyper + 1 Hypo).
  - Hyper: K, Uric a., Lipids
  - Hypo: Mg

② Other S.E:

- GIT: NVD.
- Neuro: Headache & Tremors.
- Musculoskeletal, Arthritis & Myalgia.

---

③ • Contraindications: (اكيد)

- Uncontrolled HTN.
- Renal impairment.
- Hepatic
- Current or PH. eg Excessive phototherapy ?? (↑ Mg, r. K)
- Mg
- pregnancy & lactation (C)

• Drug interactions: (CsA Metabolised by hepatic CYP3A4)

(A) inhibitors of Cyp3A4 → ↑ CsA level!

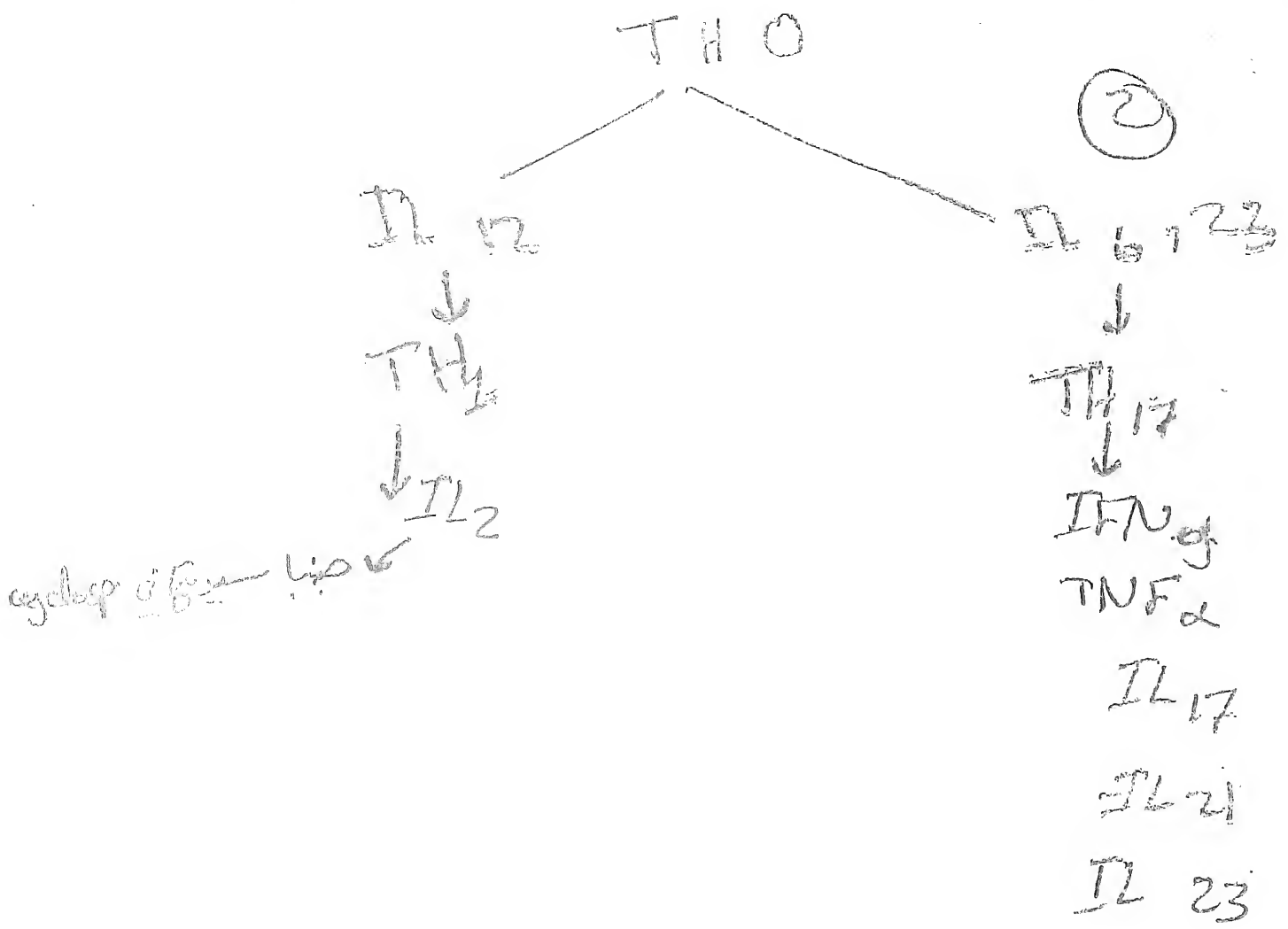
CsA is Metabolized by Cyp 3A4 & also inhibit it

Antib:
- Erythromycin
- Cipro.
- Cephalosporins
- Doxy.

- Protease inhibitors
- CCB
- Cimetidine

Grapefruit.

Antif:
- Ketoconazole, Itraconazole, Fluc.
- SSRIs


TH0
TH2
IL2
TH17
IFNg
TNFα
IL17
IL21
IL23

(B.) CYP3A4 Induces ⟶ ↓ CsA level:

- Rifampicin
- Griseofulvin
- Bexarotene
- Carbamazepine
- Nafcillin
- Tetracycline.

(C.) Drugs that may ↑ risk of Nephrotoxicity.

- Aminglycosides
- TMP/SMX
- NSAIDs
- Immunosuppressives.

• Monitoring Guidelines: (see S.E)

(Invs)

Pre ## Screening

- HX & exam: To exclude < Inf / Tms
  - B.P قياس
  - Kidny function T. (BUN & Mc. urine exam.)
  - Liver.
  - CBC.
  - uric acid, Magnesium & Electrolytes & lipids.
  - Pregnancy test.

during ## Monitoring

(as in pre ## Screening).

"ينشرف المريض كل أسبوعين
أول شهرين ثم كل شهر
مع متابعة الضغط والتحاليل"

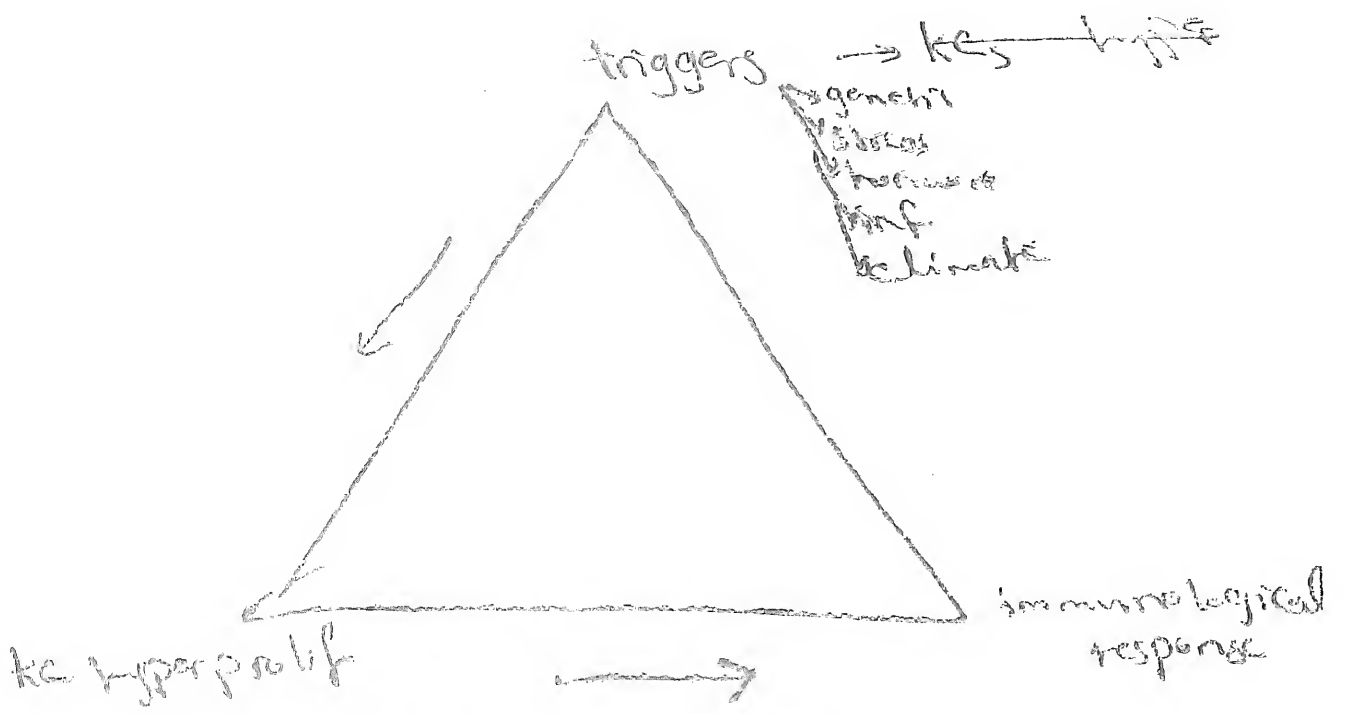
if ## For > 6ms:
1. Creatinine clearance
2. CsA level
Renal Biopsy (rare). Needed

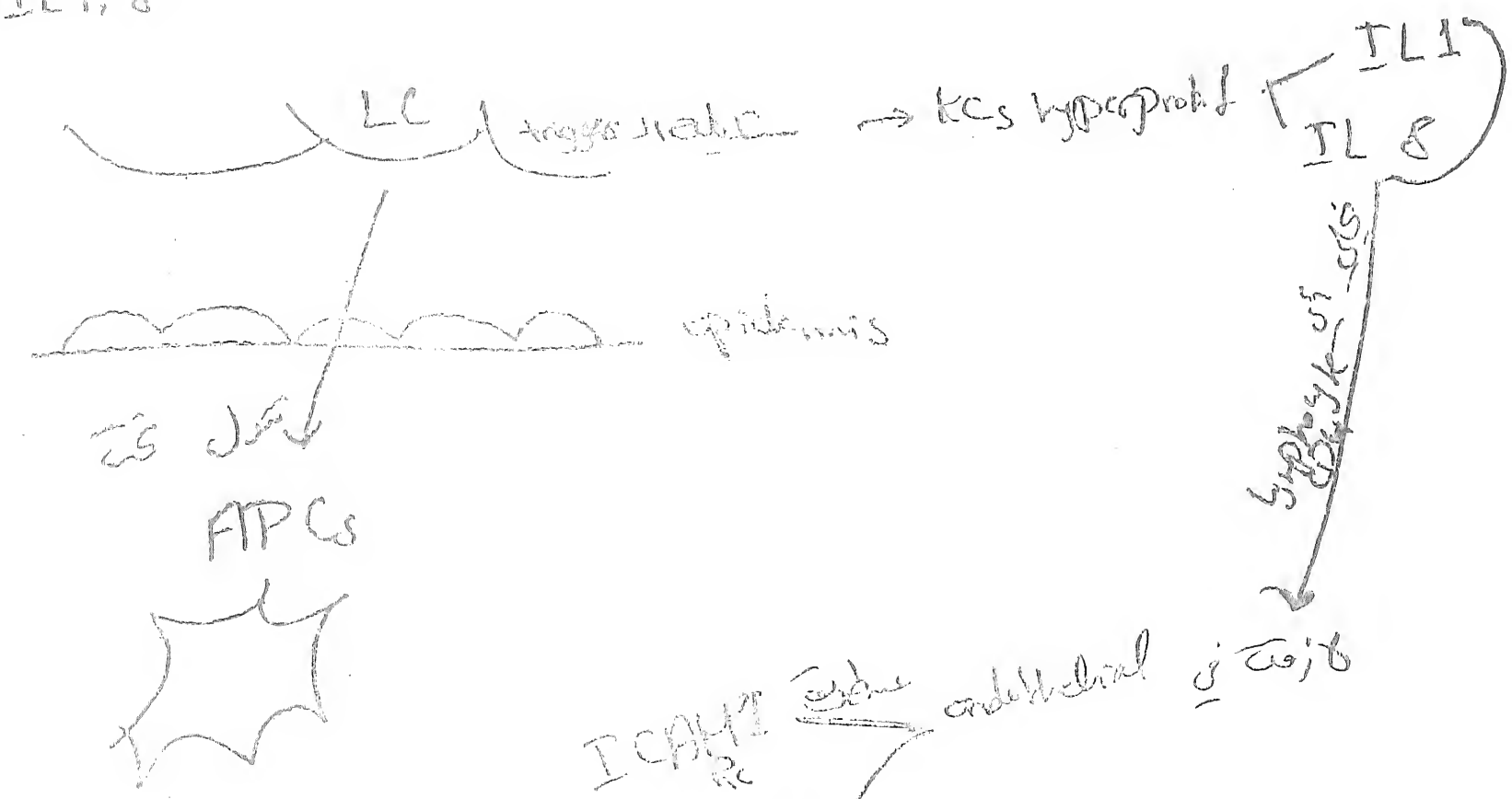
NB: 1. if HTN occured: → (give CCB):

لو اتعلق
لو ريأسي على

- Nifedipine ✗
- (DHPCCB) → : ISradipine (better > Nifed. because don't cause gingival Hyperplasia).
- ~~Non~~ DHP: diltiazem & Verapamil (not recommended (d.t) alteration of CsA level).
- * avoid (K⁺) sparing diuretics why??

Pathogenesis





Serum creatinine rises >30% above patient's baseline

↓

Repeat measurement within 2 weeks

↓

Creatinine is sustained at >30% above patient's baseline

↓

Reduce CsA dose by at least mg/kg per day
(for at least 1 month)

↓

Creatinine decreases to <30% above patient's baseline

↓

CsA treatment can be continued at new dosage

Creatinine remains > 30% above patient's baseline

↓

Stop CsA treatment

↓

Creatinine returns to within 10% of patient's baseline

↓

CsA treatment can be resumed at lower dosage

Figure 11-3: Steps to follow with rising creatinine. Adapted from Berth-Jones and Voorhees.[62]

NB

CsA

- Rapid Clearing
- ↑ Hair growth
- affect Kidney
- ↑ K+ & ↓ Mg+
- Preg.(C)

Aciretin

So:

- Slow Clearing (used to maintain Clearance induced By CsA)
- ↑ Hair loss.
- No effect on Kidney.
- -ve.
- Preg. (X)

But Both
↑↑ lipids.

* Biologics *

Targeting

- B-cell
  - ↓
  - Rituximab
- T-cell
  - ① Inhibitor of trafficking
  - ② Inhibitor of T cell activation
  - ③ Anti TNF_α
  - ④ Anti IL_{12}

Biological Immunotherapy (Targeted Immuno modulators)

(Bioengineered Immunomodulators)

Def. ⇒ Bioengineered Molecules That Target Specific steps in pathogenesis of several immune mediated disorders

as: Psoriasis
Ps. arthritis
Rhoid arthritis
Pemphigus
Crohn's
B cell Lymphoma.

They work by one or more Mechanisms:

1. Elimination of pathogenic T. cells
2. -- T cell activation
3. -- T Cell Trafficking
4. -- Cytokines (TNFα)
5. Changing the immune Profile from (Th1) → Th2
6. Eleminating Pathogenic B cells.

Biological Immunotherapy may be directed against

- Pathogenic T cells.
  - Inhibitors of T-Cell Trafficking
    - Efalizumab
  - Inhibitors of T-cell Activation
    - ✓ Efalizumab
    - ✓ Alefacept
    - ✓ Ustekinumab
  - (3) Anti-TNFα
    - ✓ Etanercept
    - ✓ Infliximab
    - ✓ Adalimumab (humera) 2800 L.E
  - (4) Anti-IL 17 → Secukinumab. 4000 L.E
- Pathogenic B cells
  - Rituximab
    - Used in → B Cell Lymphoma
      Rhoid arthritis

• Inhibitors of T-Cell Trafficking

• Efalizumab

↓

Anti CD11a

(CD11a is a component of LFA-1 on T cells & Endothelium).

↓

Blocks interaction bet LFA-1 (on T cells) & ICAM-1 (on T cells → -- activation; Endothelium → -- Trafficking)

∴ So Efalizumab has double Mechanism of Action

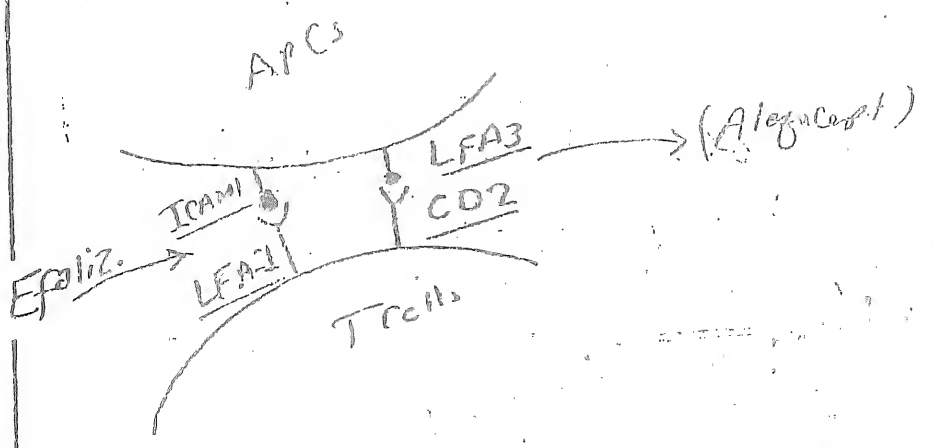
• Alefacept

↓

Anti CD2

↓

So Blocks Interaction bet CD2 (on T cells) & LFA3 (on APCs)



أمتنعوا عن السوق

• What is the Composition of these Molecules??

① Alefacept → Human fusion protein = LFA-3 + IgG-Fc

يعمل على CD2 فيمنع إتحاد (APC على) LFA3 مع CD2 الـ

② Efalizumab → Humanized (Mouse + Human) monoclonal Antibody that block CD11a → -- LFA-1 & ICAM-1 interaction.

• Efalizumab : Severe Neurological complication (PML) تم سحبه من السوق سنة 2009

• Alefacept : Risk of Mg إلى 2011 تم سحبه من السوق

Biologics : أدوية

CEPT

Fusion protein

IgG1

as in etanercept

IgG1

LFA3

bind to CD4

IgG1

etanercept

TNFα Re

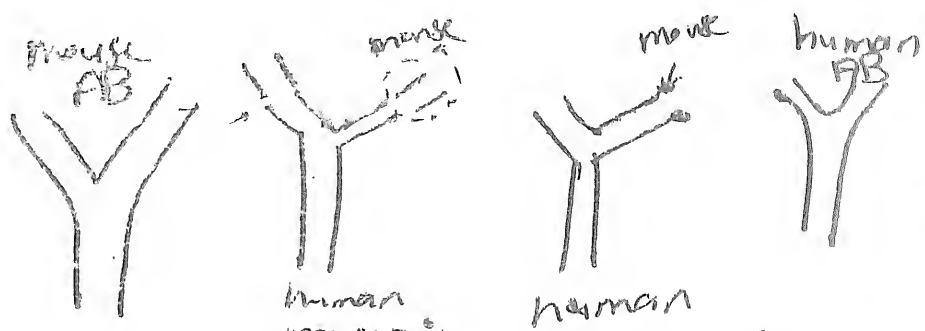
TNFα يثبط
in circulation

MAB

* mono clonal AB

أجسام تنتج من خلية واحدة Ab

→ Blocking AB



① mAb → monoclonal AB from mouse

② cimab → chimeric from human

③ kimab → kimeric

④ humab → humanized

mouse → allergy يسبب

kimeric

Xolair → omalizumab →

يسجل allergy. تطعيم 30% فقط مسجلة لهيدة بطيئة

Anti TNF-α

Etanercept

Fusion protein composed of: (TNF-α Receptors) + IgG1-Fc

TNFα ↑ إفراز

اللي في الدم وبالتالي تمنع ارتباطها مع مستقبلاتها الطبيعية على سطح T cell.

Infliximab

Chimeric Monoclonal Antibody

That binds to TNF-α → prevent interaction of TNF-α with their Receptors.

تشغل بعض إنزيمات الجسم لكنها تختلف في التركيب.

Adalimumab

Human Monoclonal Antibody

To TNF-α, Thus preventing their interaction & surface Receptors

Ustekinumab: Anti IL12 & 23 → TH17 diff ↓

Block diff of TH1 ↓ IL17

NB

- Alefacept & Etanercept → Fusion protein
- باقي → Monoclonal Antibo...

كده اتكلمنا عن الميكانيزم والتركيب

الجدول

(-cept = fusion protein)
(-mab = monoclonal Ab Block)

Agent	Target (Anti:)	Structure
Alefacept	CD2	• Fusion protein
Efalizumab	CD11a (Part from LFA-1)	• Humaized (zumab) Clonal Ab.
Etanercept	TNF-α (Soluble form)	• Fusion protein.
Infliximab	TNF-α (Soluble & membrane bound)	• Chimeric Antibody (ximab)
Adalimumab	TNF-α (sol. & bound)	• Human Antibody (umab)
Ustekinumab	Anti P40 Subunit of IL12/IL23	• Human Antibody. (umab)

Discussion of

- Indications.
- Contraindications (C.I)
- S.E
- pre-tt invs (Baseline)
- during tt Monitoring (Follow up)
- Doses
- الأسماء التجارية

Indications in Ps:

① Mod-severe Ps. Eligible for systemic therapy

② When Systemic tt < failed or Contraindicated

Ex: (liver) or preg: DMARDs: Disease modifying anti Rheum Drugs

③ Psoriatic arthritis: after failure of

Contraindications

General

- **Absolute**
  1. Inf (Viral, Bact (TB), Fungal)
  2. ↑ risk of sepsis
  3. Immunosuppression
  4. Hypersensitivity
- **Relative**
  - Pregnancy < Anti TNF & Alefacept (B), Efalizumab (C)
  - Malignancy (PH (3) Last 5 yrs)
  - Excessive UVR or Photochemotherapy (BCC or SCC يدخل)
  - Hepatitis B (Give tt or Prophylaxis to prevent Reactivation)

Selective

- Efalizumab: leukocytosis, lymphocytosis or Thrombocytopenia
- Alefacept:
  - CD4 < NL
  - HIV → CD4 ↓
- Anti TNF ↓: Autoimmune
  - ANA +ve CTDs
  - AICTD
  - CHF
  - MS (also the FI multiple sclerosis)
  - Blood dyscrasia
- Ustekinumab B1
  - BCG ⊕ the past 12 m.
  - live attenuated vaccine

• Side effects.

- **Alefacept** →
  - Local Reactions at site of injection (Commonest)
  - ↑ Mg. Risk.
  - ↓ CBC
  - ↓ Lymphocytes
- **Efalizumab** →
  - Flu like symptoms (Fever, Headache, Pain, Chills, GIT dist.) → Common in the 1st few wks.
  - Blood Toxicity (Hemolytic anemia & thrombocytopenia).
- **Etanercept** →
  - Local Reactions at site of Injection (Commonest) (Erythema, pruritus, Pain & Swelling)
  - ↑ Reaction
  - ↑ infection
  - ↓ Lymphoma
  - ↓ L.E. (Anti-TNFα induced SLE)
- **Infliximab** → (Infusion)
  - Infusion-related Reactions (Commonest): (itching, urticaria, pain, HypoTN & HTN)
  - ↑ infection: Pneumonia, Cellulitis & Sepsis.
  - ↓ Lymphoma & Mg (±)
  - L.E. (±)
- **Adalimumab** →
  - ↑ incid. of Mycobact. Inf. & opportunistic Inf.
  - Lymphoma & Mg (±)
  - L.E (±)

Alefacept	Local Reaction
	Inf. opp. (mycobact)
	Mg & Lymphoma
	LE. drug induced Lupus
Efalizumab	→ Sepsis, Viral Meningitis, Hemolytic an… Progressive Multifocal Leukoencephalopathy (…) (Local management)

Pre-Tt Assessment (Base line Inv.)

- Efalizumab & Alefacept → CBC & differential T cells (CD4)
- Anti TNF-α → Tuberculin Test (..PPD) or Quantiferon-TB Gold
  - chest X-Ray (optional).

During Tt Monitoring (Follow up Inv.) [أثناء العلاج]

- Alefacept: CD4+ assessment ✓ ..... (كل ٣ شهور)
- Efalizumab: CBC (كل شهر)
- Anti TNF-α: Tuberculin test & CXR (كل سنة)

Doses (كفاية: Etanercept, Ustekinumab, Adalimumab) (SC)

- Alefacept: IM (15 mg) or IV (7.5 mg) — كل أسبوع لمدة ١٢ أسبوع، ثم كل ٤ أسابيع بعد ذلك
- Efalizumab: SC. 1 mg/kg/w. (For 12 wks)

- Etanercept (Enbrel): SC. 25 mg Twice/w for 12 wks then 50 mg/w. (For 12 mos)
- Infliximab: slow IV infusion: 5-10 mg/kg at 0, 2, 6 wks then /8 wks
- ✓ Adalimumab: 40 mg SC/2w
- Ustekinumab: <45 kg: 45 mg SC, 4 wks dose, then /12 wks
  - >100 kg: 90 mg " " " "
- ✓ Secukinumab: 300 mg SC at 0, 1, 2, 3, 4 wks Then 300 mg/4 wks. (Cosentyx)

- 2 EU → SC
- Alefacept → IM or IV
- Infliximab → IV

- Alefacept: Amevive®
- Efalizumab: Raptiva
- Ustekinumab: Stelara

- Etanercept = Enbrel
- Infliximab: Remicade
- Adalimumab: Humira
- Secukinumab: Cosentyx

Rituximab

- Def → Chimeric Monoclonal Antibody; against CD20 (IgG1) on the surface of B cells. (Not plasma cells)
- Mechanism: Binds to CD20 → B cell apoptosis & depletion (NL & diseased)
  - Complement mediated Antibody
- Indications:
  - B Cell Lymphoma.
  - Rhoid arthritis.
  - *FDA: Wegner's granulomatosis, Microscopic PA, Polyangiitis (Cs)
  - Pemphigus (vulgaris & Paraneoplastic)
  - Bullous Pemphigoid (BP)
  - SLE.
  - DM.
  - Vasculitis.
- Dosage:
  - Lymphoma: 375 mg/m² IV for 1-2 ms
  - Rh. Arthritis: 1000 mg I.V. for 2 Ws.
- S.E:
  - Anaphylaxis & death: in 24 hrs.
  - ARF
  - SJS
  - TEN: Toxic epidermal necrolysis
  - Mg
  - Others:
    - FAHM, Chills
    - Itching
    - Rash
    - Urticaria & Alopecia.
- CI → Allergy
  - HBV.
  - Cardiac pt.
  - Inf.

C.I ē Active Inf.

Leflunomide (Arava / Avar) (R)

sy: Arava

- one of DMARDs: "Disease Modifying Anti Rheumatic Drugs"

- Indications: (1) Rheid Arthritis.
  (2) psoriatic "
  (3) Psoriasis.

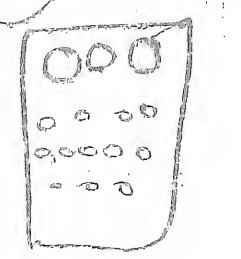
- Mechanism: -- dihydroorotate dehydrogenase → -- Pyrimidine synth → Antiproliferative.

- dose: 100 mg ld for 3 days, then 10-20 mg ld

  - Response: ē in 4 wks
  - Maxim. ": 4-6 wks.

- S.E: GIT
  - Pruritus, Rash, HTN.
  - Hepatotoxic.
  - Alopecia.
  - Pancytopenia.

- Liver
- CBC > تابع



البريطي 3 حبوب بـ 100 mg متقطعين وباقي الشهر 10 mg يوم

Indications of Systemic Cs in Ps

1. persistent uncontrolable Erythrodermic Ps. causing Metabolic problems
2. GPP: if other lines failed or C.I
3. Pustular Ps. of pregnancy
4. Hyperacute Polyarthritis.

• Other therapies

(1) Combination
(2) Rotational
(3) Sequential

1- Combination

Contraindicated combinations

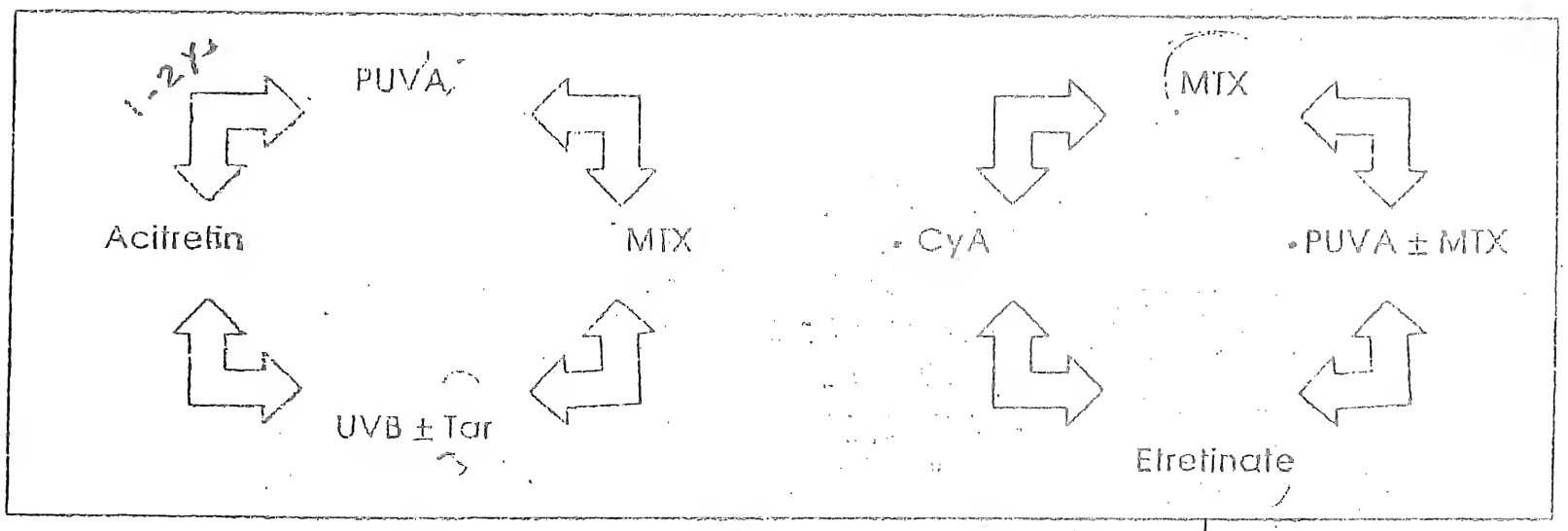
- Acitretin and CyA? Accumulation of CyA ⟶ CyA inactivation by cytochrome P-450 system can be inhibited by acitretin.
- Hydroxyurea & MTX or azathioprine.
- CyA + PUVA ? ↑ occurrence of SCC. & MTX & PUVA → SCC
- Cola tar + PUVA? Significant phototoxic responses.

Combination with the biologics

- Etanercept + MTX. CyA. Acitretin.

2- Rotational therapy in psoriasis

- This facilitates long-term treatment & minimizes chronic toxicity by rotating to different treatment regimens before significant "individual drug" toxicities occur.



Selection of rotational therapy:

- Each of the 1ry agent therapies (PUVA, methotrexate, etretinate, UVB & cyclosporine), should be used in rotation for only 1-2 yrs to avoid the risk of appearance of side effects, e.g. skin cancer with PUVA.
- If a pt was able to tolerate 2 or 3 of the therapies, it might take 4-6 yrs before returning to the initial treatment, thus reducing the cumulative toxicity from each individual therapy.
- If the 1ry agents are no longer effective, then 2ry agents should be considered.

3. Sequential therapy

Calcipotriol
cyc + Acitretin

Example of PASI score

	Head & Neck	Upper ext.	Trunk	Lower ext.
Erythema (0-4)	4	4	4	4
Scale (0-4)	4	4	4	4
Induration (0-4)	4	4	4	4
Sum (E+I+S)	12	12	12	12
Body surface area (1-6)	6	6	6	6
Sum x Area	72	72	72	72
Area multiplier	0.1	0.2	0.3	0.4
Sum x Area	7.2	14.4	21.6	28.8
PASI total	72			

BSA: (0)=None, (1)=<10%, (2)=10-30%,(3)=30-50%, (4)=50-70%, (5)=70-90%, 6=90-100%

PASI

- 1–10 Mild
- 10–20 Moderate
- >20 Severe
- PASI 75 75% improvement in baseline PASI
- PASI 50 50% improvement in baseline PASI
- Static indicator: Only indicates disease severity at time of scoring
- Internal consistency is essential

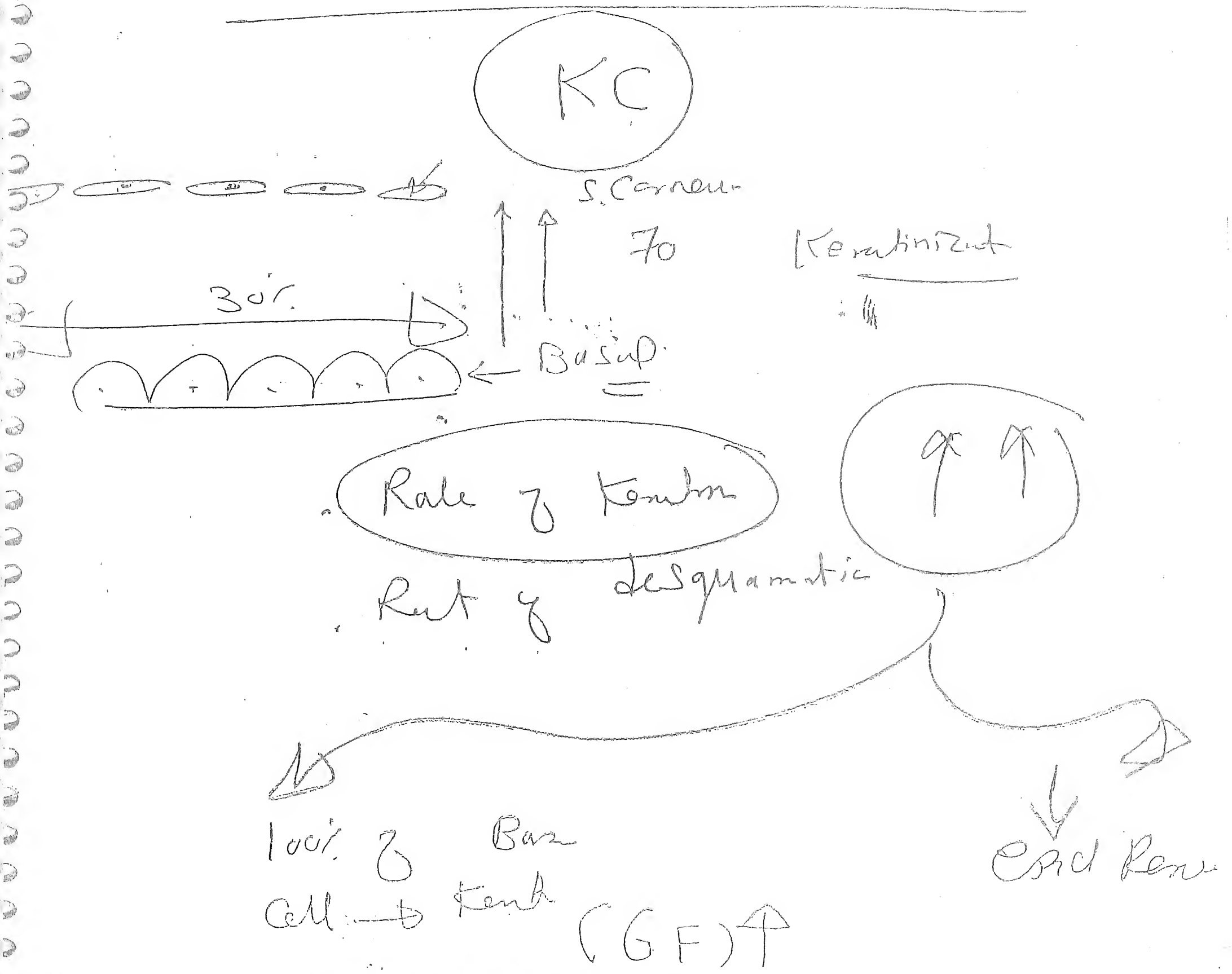
2. Sfen. Substance (P) (Capsin)

3. Inf.

4. Trauma.

5. Climate:

6. Hormones.



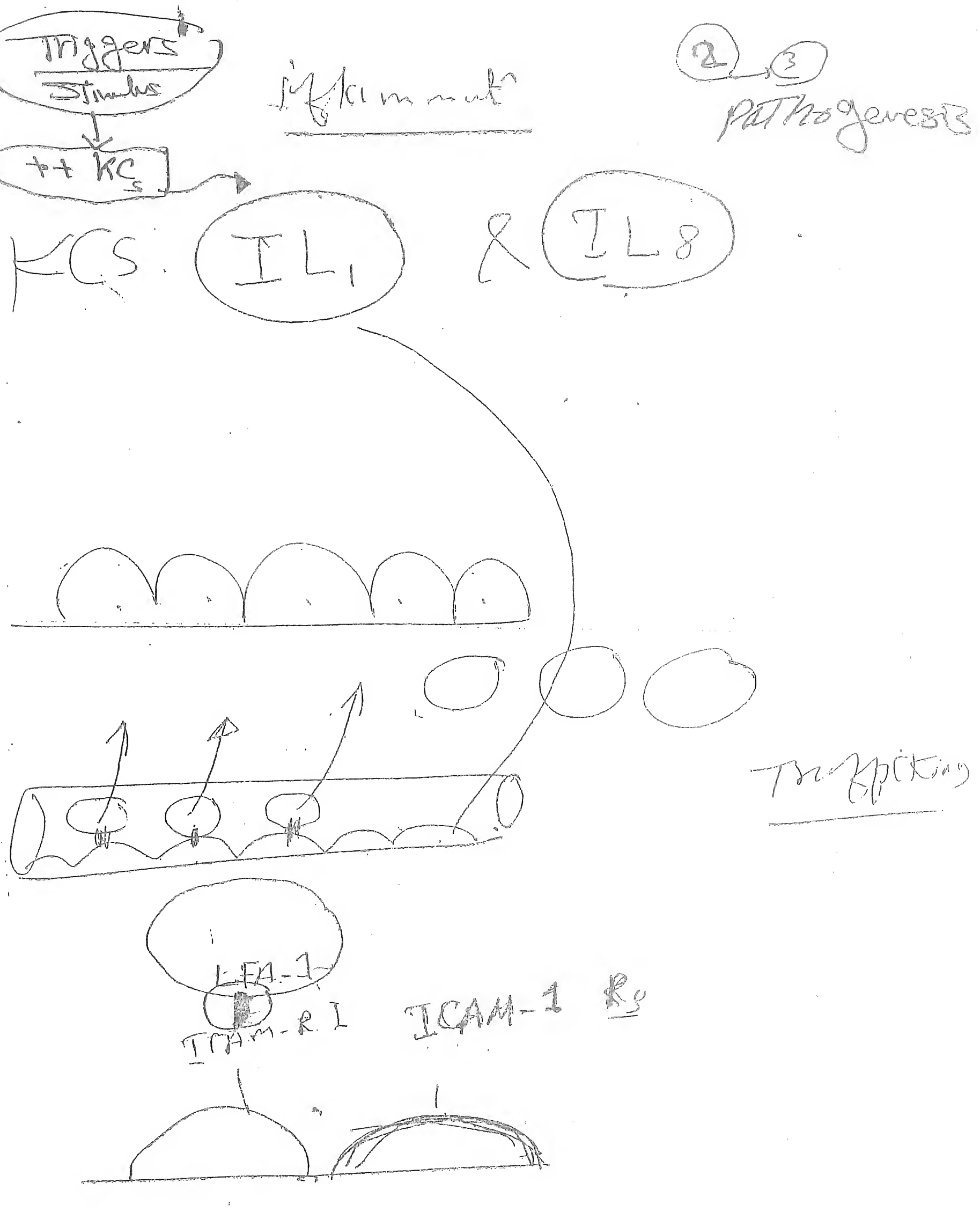
Triggers
Stimulus

++ KC_s

KCS → IL_1 & IL8

Inflammation

2 → 3
Pathogenesis



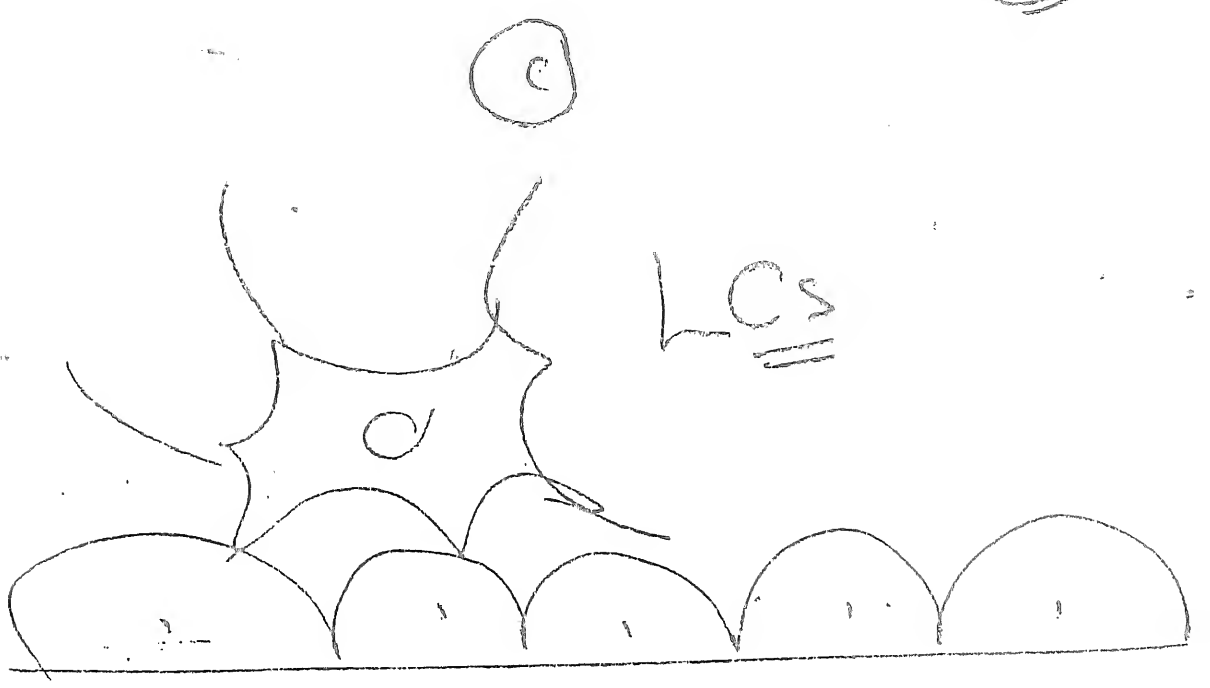
Trafficking

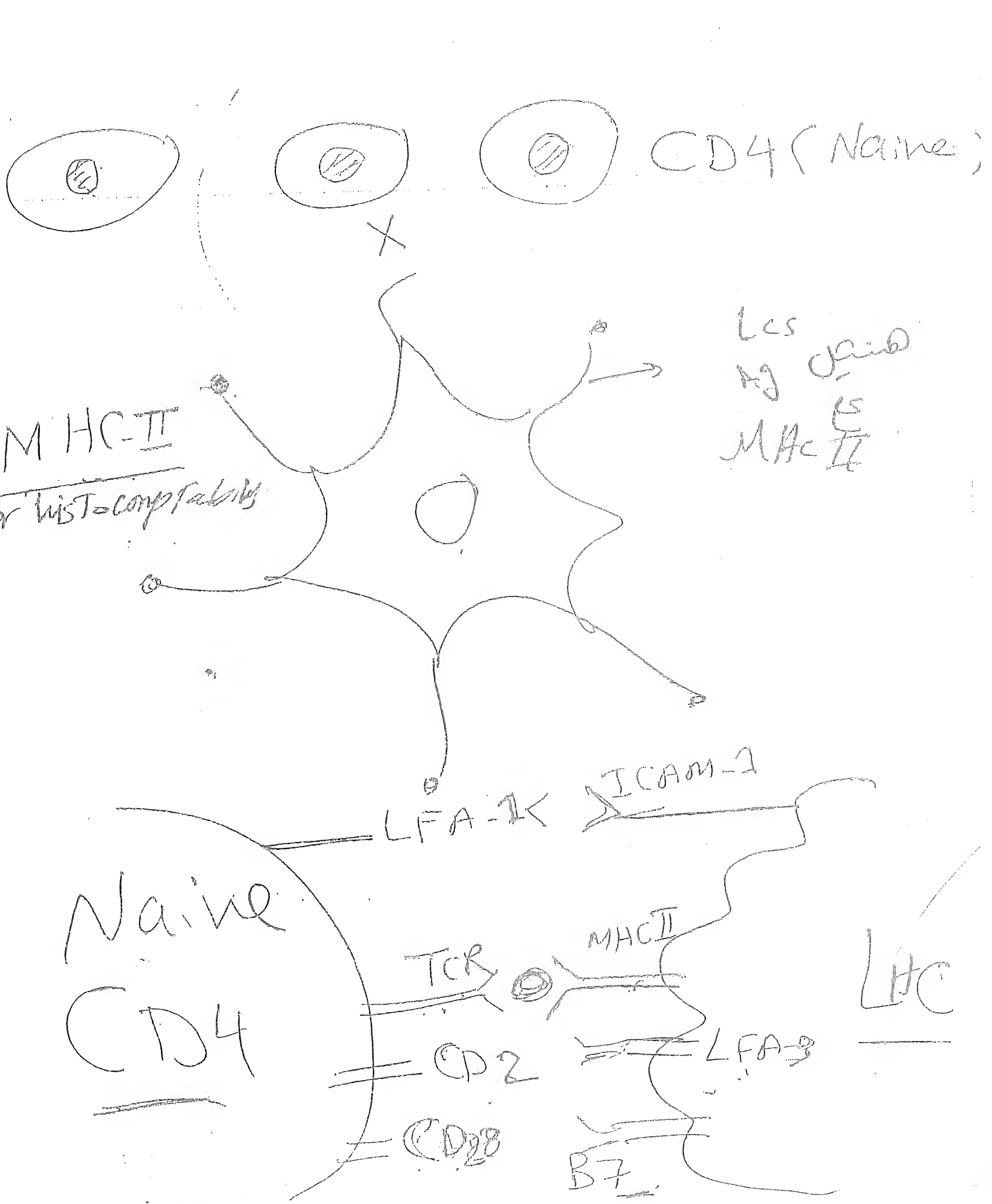
LFA-1

ITAM-R1

ICAM-1 R_5

- 5-10%
- 25-50%
- 50-75% P_3


LCs


CD4 (Naive)
X
MHC-II
Major histo-compatibility
LCs
MHC II
LFA-1
ICAM-1
Naive
CD4
TCR
MHC II
LFA-3
CD2
CD28
B7
LHC

SKin

Orthen PT

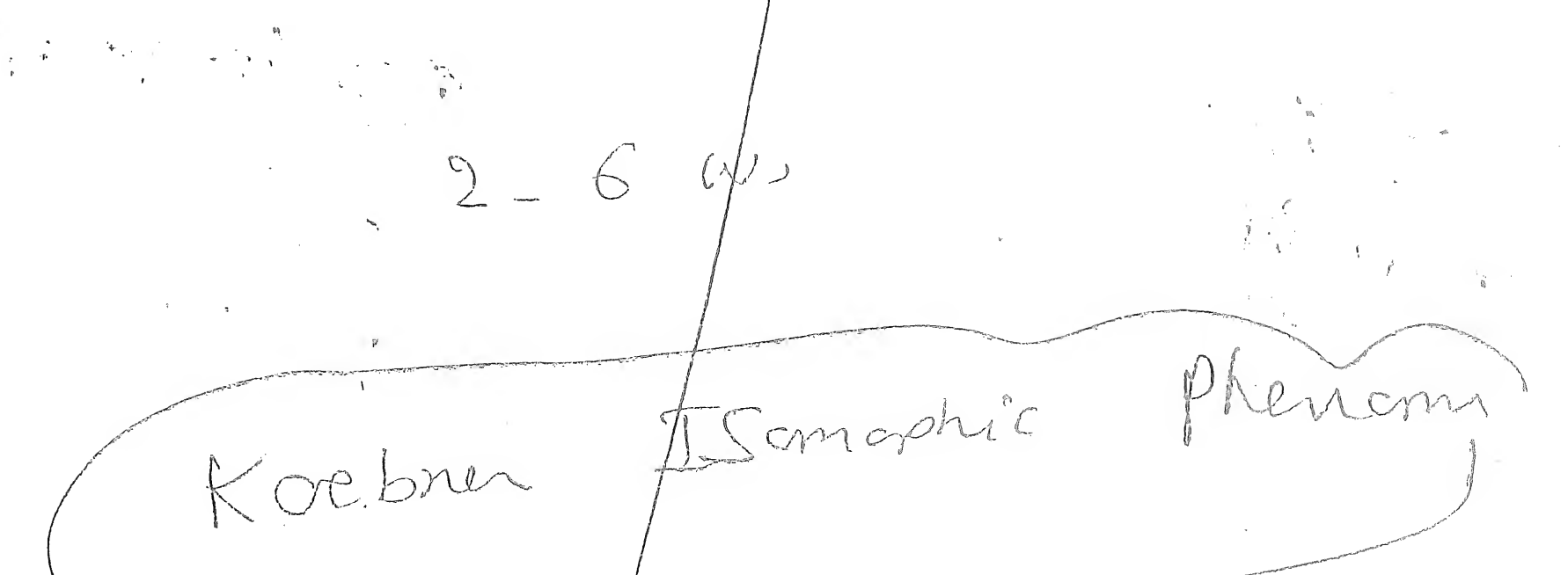
Greatage

2 - 6 (4)

Koebner Isomorphic Phenom

Surgical

PNF



(4)

CD4 (Thelper = Naive Th0)

IL12

Th1

IL2

مهم جدا

TNF α

IFN- δ

IL6, IL23

Th17

x IL17

IL21

IL22

KC

KC

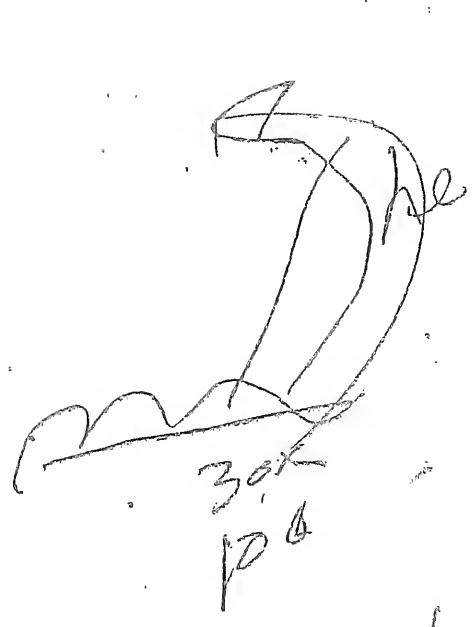
Th1

Th2

IL4

IL13

PS



Triggers

KCs

Th1 & Th17

↑ GF (3c) → (1c)

↓ Resew ↓ (7c) → 7

↓
IL2
TNF
IFN

IL7
IL21
IL2

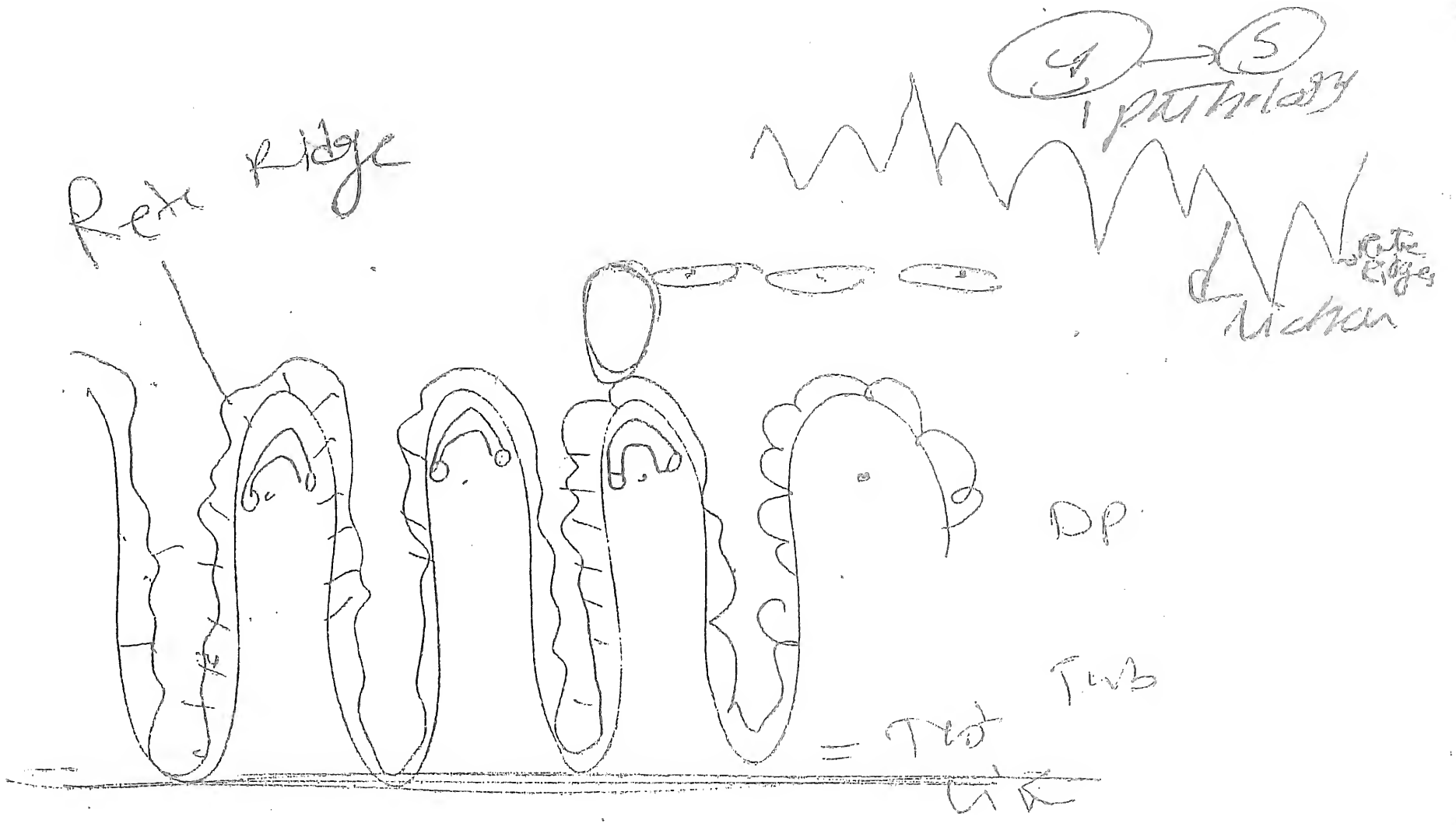
Th2

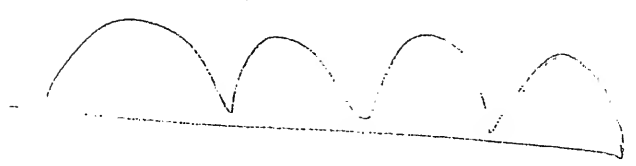
Atopy

IL4, 5, 6, 10, 13

↑ IgE

++ Eos





Pitting

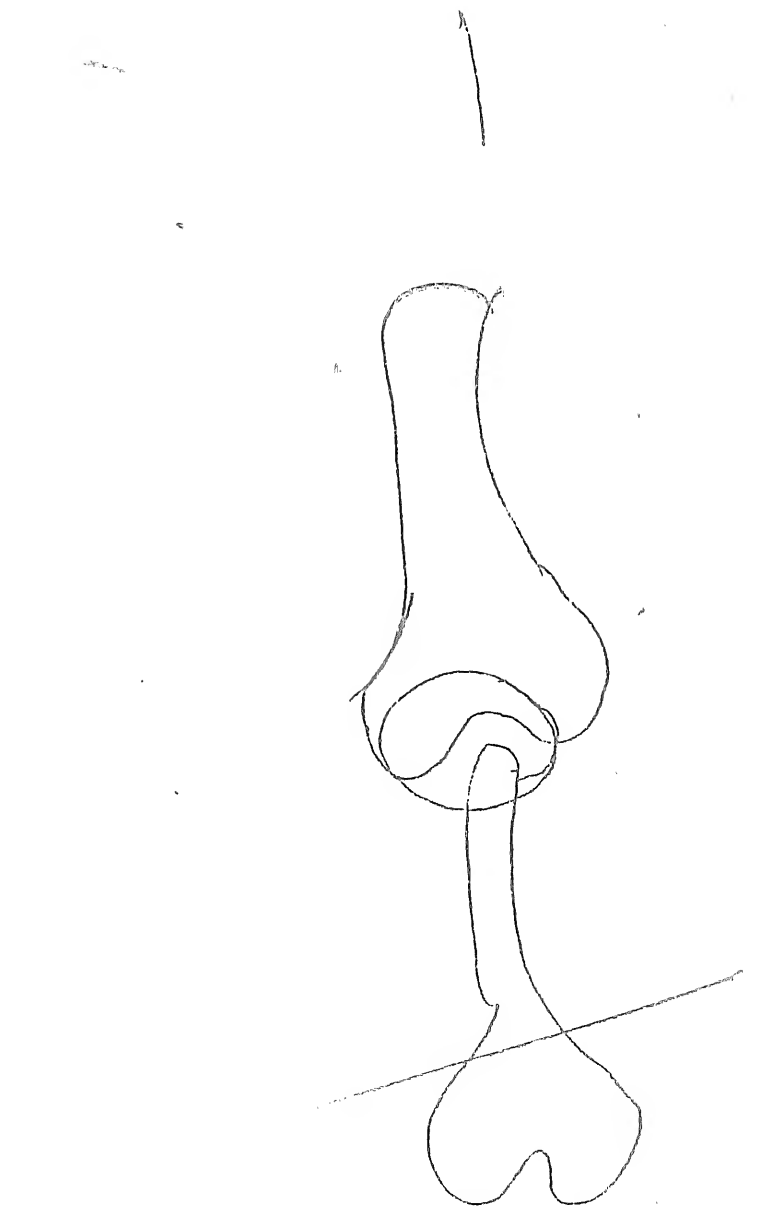
(1) Parakeratosis : Retd Nucl.

(2) Acanthosis : ↑ Thickness of Spinous cell Layer

(3) Hypogranulosis

(4) Regular elongated Rete Ridges.

(5) D-P



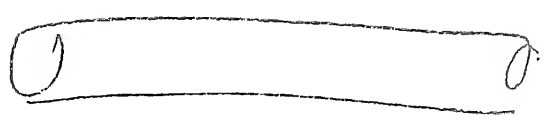
Pustular

PS

Munro

Spongi form

Pustule b Kogoj



Date / /

Subject داصلى

التاريخ / /

الموضوع Psoriasis

① surface area.

② PASI score ممكن oral.

acc to surface area → ٢٥٪ in palms → mild

but it causes distress → so it considered severe psoriasis

in ↳ face

↳ palms

↳ genitalia

③ location.

④ Ps. activity

⑤ Psychological impacts

⑥ financial.

++

15-20 L.E. ① methotrexate ② Acitretin

③ cyclosporine ④ Biological

* methotrexate → 20 LE / month

folate مثبط إنزيم → Dihydrofolate → tetrahydrofolate

(vit B complex - vit B9)

thymidilate ← purine

- Dihydrofolate reductase ← enzyme في DNA, RNA synthesis

- Dihydrotemate synthetase

- thymidilate synthetase

Date / / التاريخ / /

Subject the methotrexate acts on:- الموضوع

→ malignant cells

→ lymphoid cells

→ BH cells

→ hyperproliferative KCs

* ① competitive inh. of Dihydrofolate reductase enz.

② - inhibition of KCs proliferation

- immunosuppressive → rather than → Anti proliferative

lymphoid cells (1000 times) → KCs

③ Anti inflammatory

④ S-adenosick

* thymidylate synthetase inhibited by methotrexate.

مثبط

partial & reversible

وزن oral (2.5 mg/tab)

(IV-IM-SC

↳ rarely topical

oral ← total dose 15-25 mg/week (0.2-0.4 mg/kg/w.

by 3 per week schedule

IM → single dose

جرعة واحدة powder في

1cm ← 50 mg في vial

5cm ←

Give vial → when GIT upset occur

↳ when I reach only 20 mg & no response

↳ dermatogenic → malabsorption

in white emp. ↑ ↳ benign

↳ psoriasis

NB * methotrexate is hepatotoxic
& metabolized by kidney

Date / / التاريخ

Subject الموضوع

injection → Pre-tt investigation → CBC
- liver → hepatotoxic → HCV, B
- renal → excreted by kidney

SGPT, SGOT, albumin, Bilir

- pregn.
- chest: X-Ray
- HIV

we can give it to renal failure by adjust dose

* test dose → vial → 5mg → IM → 1 week → stop MTX BN dep. → Pyrexia if repeat inv.

if → Normal → every 1w add 2.5mg.
acc. to efficacy & SE

inv. every 2w.

SE

→ keep him at this dose to 1-2 months
then withdraw 2.5 /w.

25 → change drug.

target of improvement → 6 weeks, maximum → 3 months

* indications dermatology → FDA → PS. → severity dyn
non FDA →

- BC → anemia → use
severe impairment X
- liver → severe impa
active HCV
- renal impairment (creatine clearance)
- pregnancy & lactation (CCT)
3-6 months after preg.

Date / /

التاريخ / /

Subject

الموضوع

male → ... for 3mn after stopping

obese → risky patient ... MN

TB → ... → reactivation

S/E → G.I.T (subjective)

→ allopecia - photosensitivity, ... Cushing

→ Preg. → teratogenicity, abortion

→ lactation → immunosupp. → malignancy

→ toxicity → pancytopenia

Idiosyncrasy → fever, hepatitis

→ pulmonary dyspnea

→ rash → photosensitivity → carcinomas

→ opp. infection

obese DM Alcohol

liver biopsy → low risk → high risk

→ 3-mgm cumulative → 1.5-2 gm

dose → 1-1.5 gm

markers of fibrosis

→ amino pro collagen 3

→ elastography

* staging of biopsy *

(1) no changes (2) fatty liver, portal tract inf

(3) → A → mild fibrosis (4) cirrhosis

B → marked or severe

1 → 2

3 A →

3 B →

4 →

Date / /
Subject

التاريخ / /
الموضوع

* Interactions :-

- Dapsone, sulfonamides → inhi Dihydrofolate synthetase → more toxicity

trimethoprim (orphin) TMP.

H/f toxicity → folinic acid (leucovorin) 15mg → تتحول إلى tetrahydrofolate → Purine

عرض → DSK

عرض → thymidine

* folic a. → PO

عرض → 5mg/kg → تحول

1 tab / day

excreted by kidney → Acitretin → 10 mg / 35 mg

no pregnancy for 2 yrs → in male

3 yrs → USA

DISH → Diffuse idiopathic skeletal hyperostosis

X-Ray

A H/f of choice in psoriatic pt.

عرض → Isotretinoin in H/f pt. → تحول

عرض → efficacy

cyclosporine

HOA → تحول

Ca++ calmodulin → CD4 → LG

stim. Prod. of Calcineurine

stim. Prod. of IL2 → lymphocyte proliferation

HEGAZY NOTEBOOK

Date / / التاريخ / /

Subject الموضوع

cyclo → cyclophirin Rs كيفية عمله ← calcineurin pathway

immune suppression ← يمنع الـ IL2 Rs load

calcineurin inhibitors

as → topical, systemic

(pimecrolimus

Rs. يشتغل بنفس الـ mechanism اللي فوق

cyclosporine ← Rs الـ mechanism بتاعه

(by rapid onset of action

(category C

major life threatening ← حاجة خطيرة

cyclosporine → oxidized by liver

(metabolized

Biologics other cyclosporine ← لو حد طلع

No cyclosporine in pregnancy

⇒ nephrotoxicity

(reversible ofcourse)

⇒ HTN

⇒ hyperkalemia

⇒ hyperplasia ← gums

⇒ hypertrichosis (on eyelashes)

⇒ hyperlipidemia

⇒ hyperuricemia ← gout

⇒ hyperaggressivity

Date / /

Subject

التاريخ / /

الموضوع

*interaction →

drugs inhibit [CYPochrome Puso] → Digitalis

→ erythromycin → warfarin

→ Doxy → Anti hyperlipidemic

grapefruit → Acok → Viagra

Statin CPuso → rifampicin → digitalis → هنعل

digitalis جرعة تزيد لما اخر

Acok

cyclosporine inducer CPuso لازم

diagram الـ

*Dox seperational عشان

phax → 1month

Tracrium → 1month

[photherapy] d/BUVB → minimal SE

effects in psoriasis & lack

[topical]

Start

Dermovate

Betnovate

face, flexures → week potent s.t.

for Elidel.

vit D_3 → calcipotriol الكالسيبوتريول

Daivobet → calcipotriol + Betamethasone

maintance → for 1 y/s

Date / /
التاريخ

Subject
الموضوع

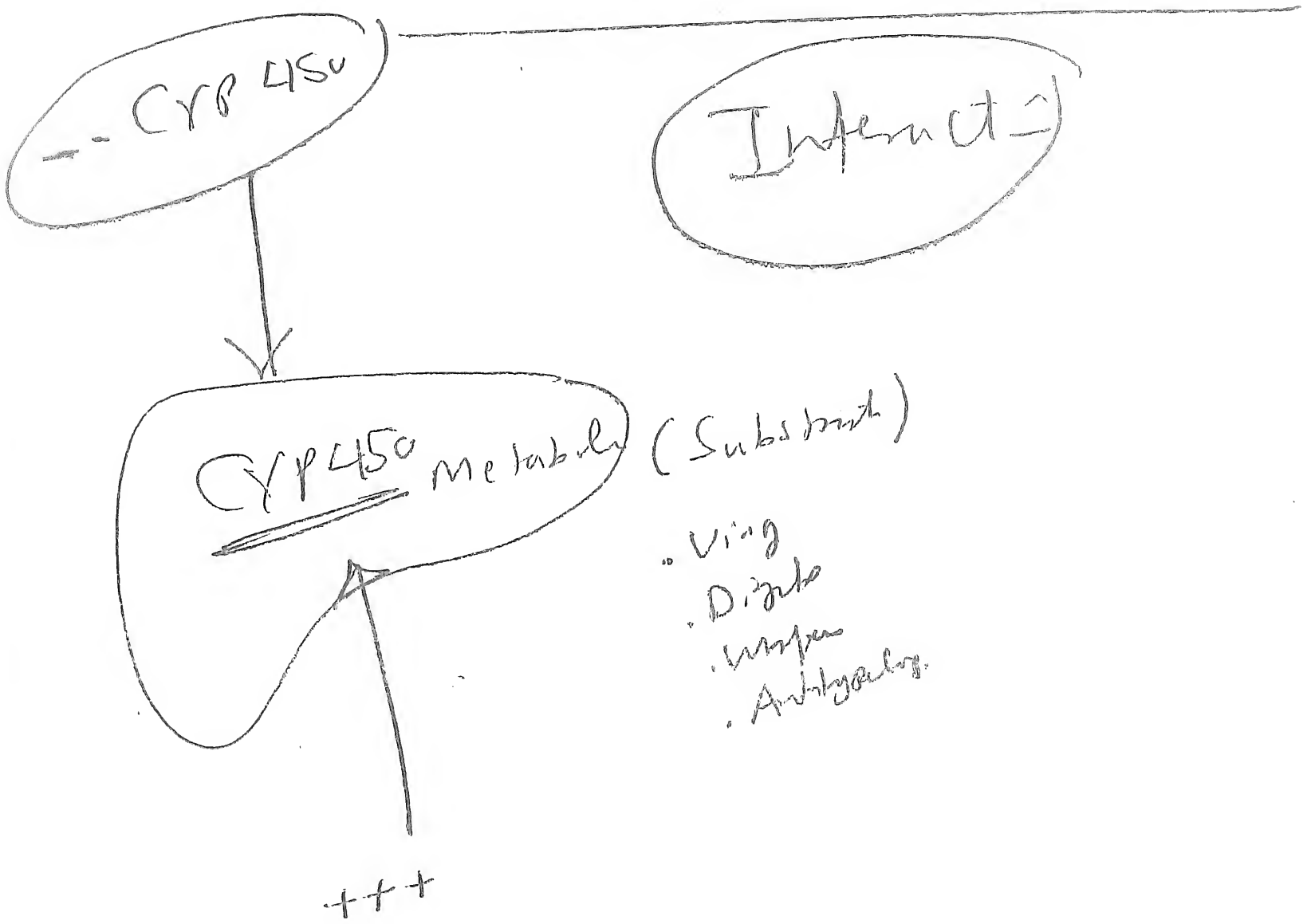
Trephiasis (Anti-cataphyte)

scalp Dysthesia
dd anxiety

Behnoufe / lotion

S.E

1. Nephrotoxicity
2. Carcinogenicity
3. Hypo — TN/Nb
   - Hypocalcemia
   - plasma Gluc.
   - Kalemia
   - Cupidemia.
   - Uremia.
4. Hypo Mg



(13)

Indwl

- EDA → PS { RaCad Ct / IH Resm. disabln Major life event
- AD

- Non FDA

(C.I) & Cyrd.

- Renal — Nephrotic
- HTN :
- Liver — Metabolized
- Preg
- lactat
- Phototh.
- Mg.
- Active Tb.
- Malb.

Inter.

12

- MTX

- falic acid

MTX

مرتبط بهبلی
حیض
مرتبط بهبلی

↓

Folic acid

Acitetin

Retinoid =

(1) Antipsoriatic

(2) ↑ KC diff

(3) Antiflam

dose 0.5 - 1 mg/Kg/d.

10 - 25 mg/d ⟶ D

11

Stage Biopsy

MTX

I → No: Observe → BMTX

Pedal Effusion

II → Pathology

III → (A) mild.
(B) Moderate.

IV → Chemo

X

Intercept.

Trimethoprim

Dihydro Reductase Synth

Folate

DHF

- Dapsone
- Sulfonamides

DHFR → THF

THF → Thymidylate Synth.

Purines

Thymidine

DNA / RNA

NSAI

Tetracycline

folinic

9

S.E

1. Subjective

2. CBC:

3. Liver:

4. Lung:

5. Skin

6. Preg & Lact

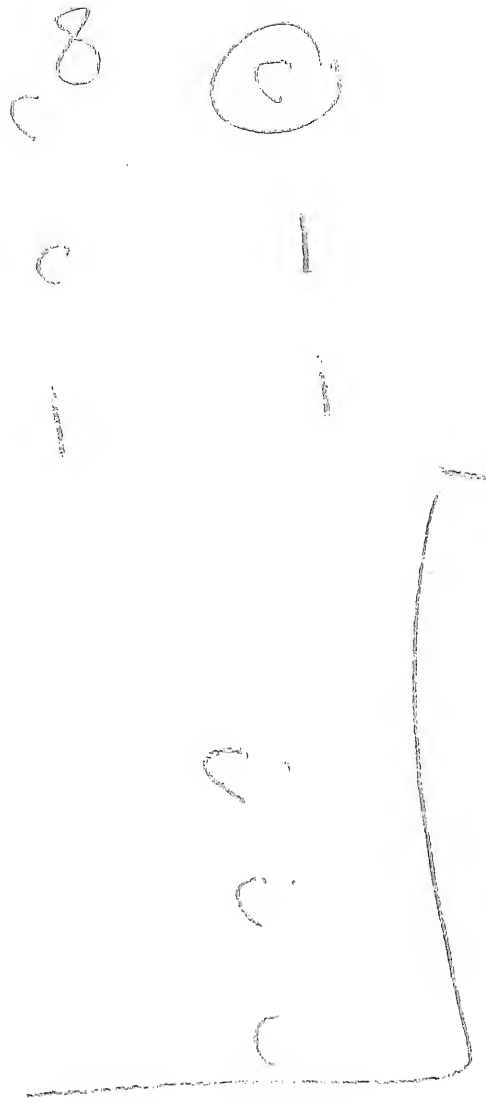
7. Idiosm

8. MTX

- High Risk — 1.5 - 2
- Low Risk — 1 - 1.5

3 - 4 gm

- Amniotic procollagen III
- Elastography



- CBC Sem Imp
- Lipid : Active Hepa
- Renal :

- Preg & lact

↓

♀ 3- 6 m.

♂ 3 mT

RISKY →

- Diabe
- Alcn
- obese
- Cardiac hered { non Ach / Hx of Prost / Hx of fam hist

- Imm
- Infect
- Active PU

MT is Competitive DHFR

① -- KC Hypersensitivity (Anaphylaxis)

② Immunosupp: Lymphocyte reaction

③ Antifolate, SAM

Thymidylate synthase MTX

Dose

Total 15 - 25 mg/w

Ac. 2 - 0.4 mg/kg/w

① GIT

② >20 mm

③ Dermatogenic

Tablet

2.5 mg

1. bkp بكرة

2. سكر

3. كحول

Inject

(IM)

Single dose

amp = 5 cm
2 cm
5 cm

Inject

- CBC
- Liver = Hepatic
- Renal = exc. by Kidney

قبل ١٢ ← Pregnancy, CXR, HIV

Test dose → 5 mg

CBC, Liver

2.5mg/kg

20mg/kg

Improved

MTX → Hepatic, Kidney

Nephro, Metabolic → CYCh

25

onset : 2-6

3 mg

Indication

FDA

No FDA

Systemic HH

MTX

Acheter

Cycl.

Biologic

MTX

↓

○ Mechanism :

Folate —(Dihydropteroate synth.)→ DHF —(DHFR)→ THF

THF → Purine

THF → Thymidine

Purine + Thymidine → DNA & RNA Synth

→ MT

① - Mg

② Lymphocyte

③ BM

④ KC

Severity Ps

< 3 : BSA

mild

Topical

3 - 10 mod.

> 10 severe Ps.

Phototherapy

Systemic

± Topical

??

Severity

(1). BSA

(2). PASI

		Head & neck	upper limbs	Trunk	lower
0-4	Ery.	1	2	4	2
0-4	Indu.	0	1	2	1
0-4	Skin.	3	0	3	2
		4	5	9	5
surface area 0-6 :		1	3	5	6
		0.1	0.2	0.3	0.4

72

0

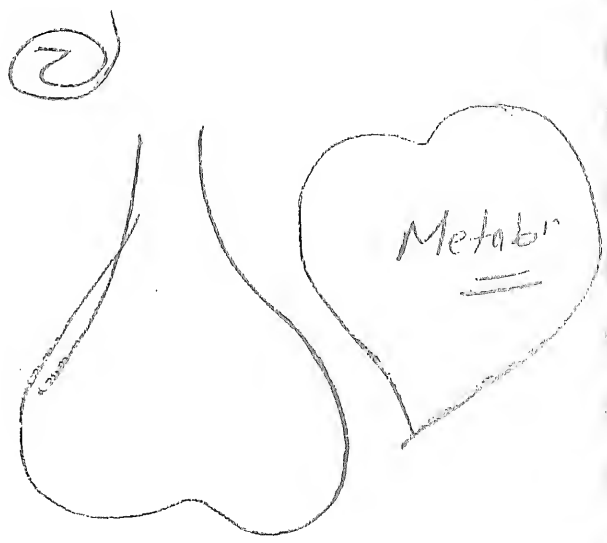
1 < 10%

2 10 - 30

3 30 - 50

4 50 - 70, 5 70 - , 6 90 - 100

Treatment of PS.



A. General Measures: Comorbidities

Obesity = Metab II

B. Topicals

C. phototh.

D. Systemic H.

E. Other

TE

. Smoking

. Drug : . Antimalind
. NSAIDs.
. BB
. كحتى ناضف
.

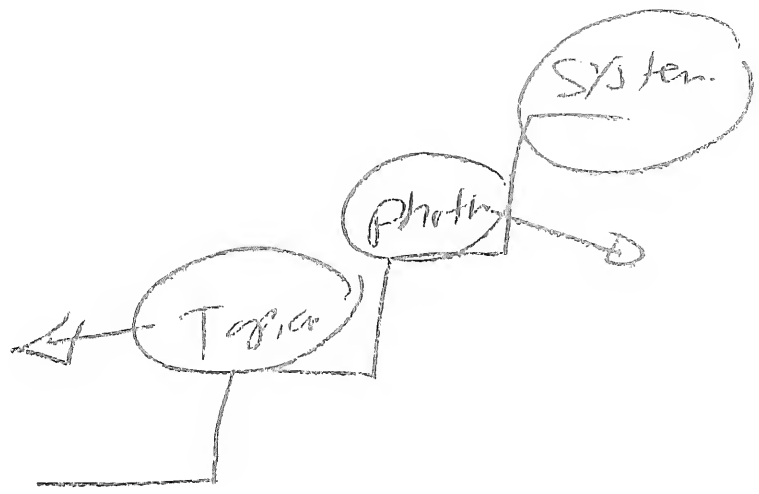
. Stress :

. Trauma

~~Contractility~~

(1) Topical

(2) ~~Systemic~~



(3) ph

Criteria

(1) . Central obesity
- Waist Circ ≥ 102 cm ♂
  ≥ 88 cm ♀

(2) . ↑ TGs ≥ 150 mg/dl

(3) . HDL . < 50 ♀
. < 40 ♂

(4) . BP ≥ 130/85

(5) . FBG ≥ 110 mg/dl

≥ 3 → Metab. Sx

Comorbidities

1. Ocular manifest. Retin.
2. Ps. Arthritis
3. Nerv
4. Crohn's & UC
5. Psychological
   . Depression
   . Suicidal
6. Metabolic Childhood

Vit D analogues

Calcif.

① Mech (3)

- ↓ K6&16
- ↑ K11,2,10
- ↓ IL8

①

S.E

Clinical:

② Inactivat

③ Calycal phos

CaCyp.

C.I

- pso
- lact
- HyperaCa
- Renal dysf.
- Abn L Bone Mtb
- > 100 gm/d

Topical Rx — mild / mod. sev.

1. CS
2. Vit. D
3. Tazarotene
4. Tar
5. Anthralin
6. SA

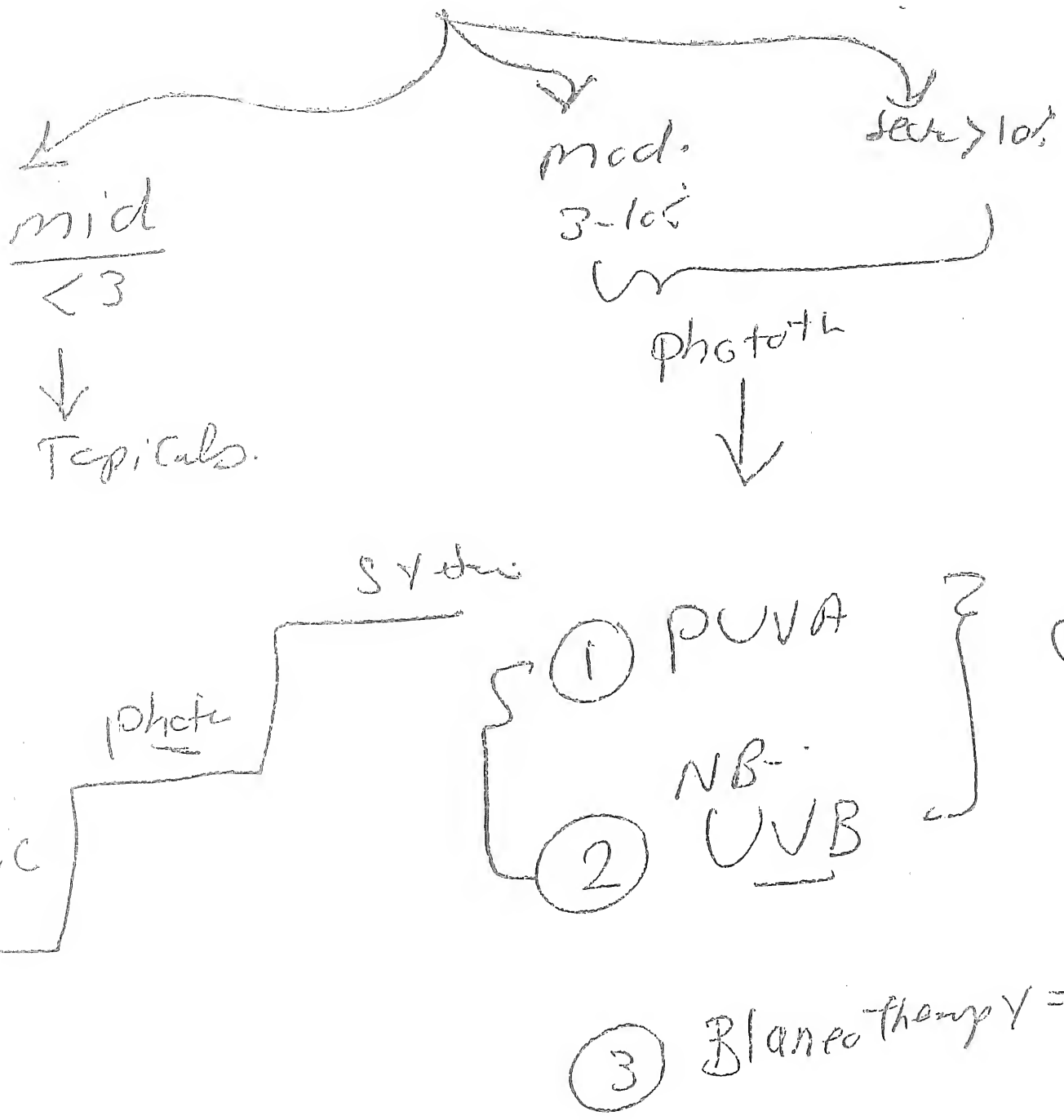
- Antifungal
  ↑ T KC ointment
- Antibiotic

>3 Tacrolimus

1. Clinic phone

2. Mainly the weekend

Phototh



3 Balneotherapy = Dead Sea th

1 Antipruritics

2 Antihistamines Immunosuppressants

3 Bland. th

4 Heliotherapy

Salt

① Alone — 2.5 m 1 Kg – 5 m

② Seq. th. — 0.5 m 1 Kg

③ Combinat –

Sequential

(1) Cleaning

Cycl Alone

7.

10 Cycl

18.
Cycl

0.5 m 1 Kg

(2) Transmit

↓ Cycl

Acke

(3) Machinery

Cicl ost → ∅

Acut & Repwn

Pre-Hospital Emergency

- CBC : Lentz
- Liver
- Renal
- Lipid Profile — Hyper
- Pregnancy test : C.I (X)

For 2 yrs (Emergency & Surgical)

= DIS H

- XRay

Alone : (Pulse)

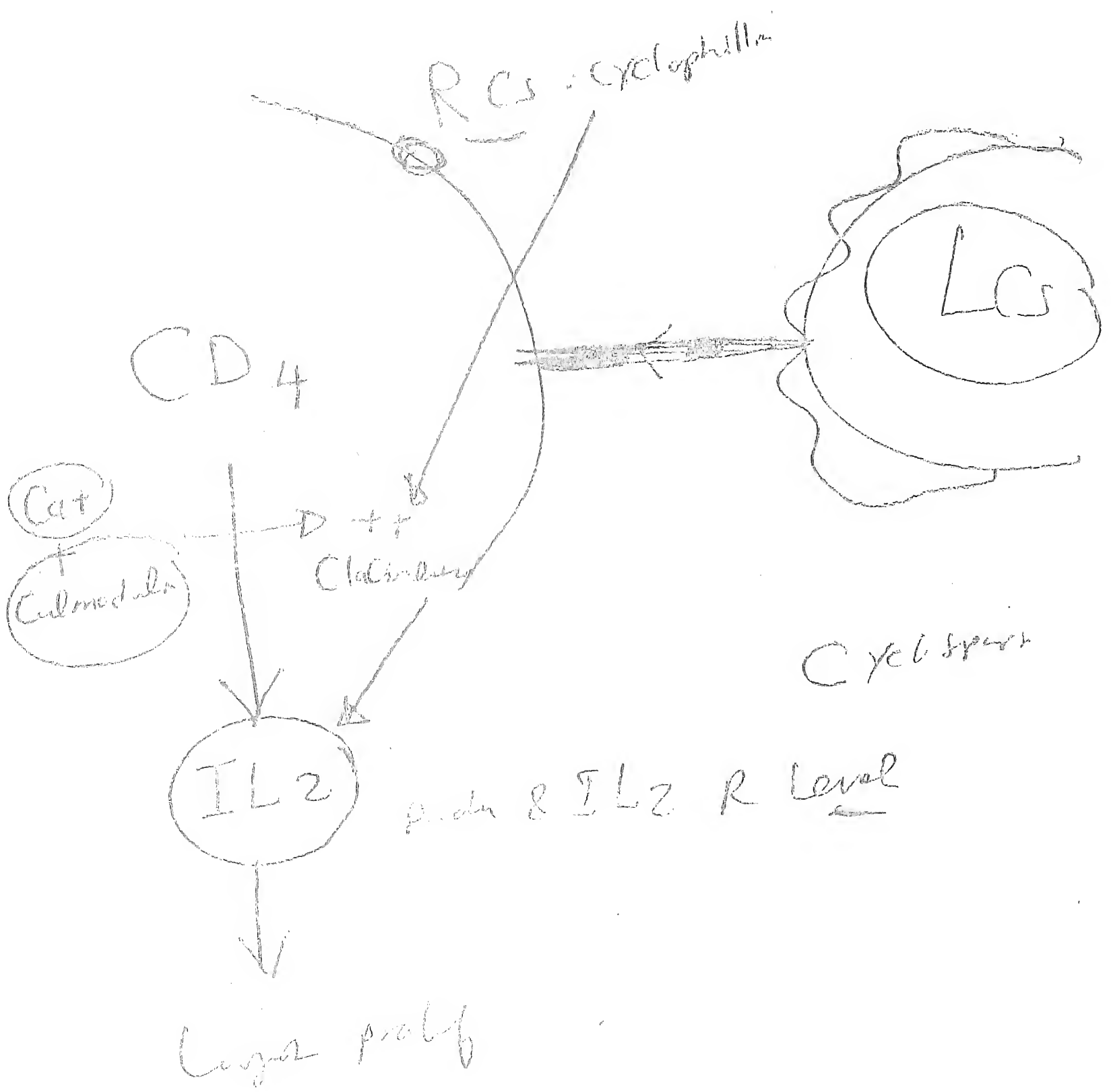
(Resp) (CVA) (Resp) (CVA)

(1) Traffic
(2) ↓ dose
(3) Ageing & Cancer

(Isotopes)

Cyclosporine = Ciclosporin

Fungus → b



Cyclosp : CalCineurin Inhibitor → ↓IL2 & IL2 R level → ↓ Imm.

CNI